Investigating the diagnosis and management of women with Endometriosis

A study of diagnostic tests, treatment strategies and quality of evidence on the management of endometriosis.

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Queen Mary, University of London

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   Curr Opin Obstet Gynecol. 2014 Aug;26(4):266-74.

2. Preoperative assessment and diagnosis of endometriosis: are we any closer?
   Hirsch M, Davis CJ.
   Curr Opin Obstet Gynecol. 2015 Aug;27(4):284-90.

3. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis.
   Hole J, Hirsch M, Ball E, Meads C.
   Lancet. 2015 Oct 24;386(10004):1659-71.

4. Variation in outcome reporting in endometriosis trials: a systematic review.
   Hirsch M, Duffy JM, Kusznir JO, Davis CJ, Plana MN, Khan KS; International Collaboration to Harmonize Outcomes and Measures for Endometriosis.
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9. Diagnosis and management of endometriosis: a systematic review of international and national guidelines.
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   BJOG: Int J Obstet Gy. Accepted Author Manuscript. doi:10.1111/1471-0528.14838

ABSTRACT SUMMARY

The aim of this thesis is to investigate the diagnosis and management of endometriosis amongst women with pain or subfertility through a series of systematic reviews and primary studies. I will also evaluate the quality of information available to researchers, clinicians and patients on the management of endometriosis.

Endometriosis is the presence of endometrial like cells outside the uterus, commonly within the pelvis. The disease is characterised by benign fibrosis and tissue invasion of endometrial like cells in surrounding structures such as the peritoneum, ovary, bowel, and bladder. The commonest symptoms reported by women with endometriosis are pain and subfertility. Non-invasive diagnostic tools have poor accuracy with the current gold standard diagnosis of laparoscopic surgery, biopsy and histological confirmation.

I performed a diagnostic meta-analysis of the most researched diagnostic marker, Cancer Antigen125 (CA-125), establishing a cut-off value that had limited sensitivity but high specificity with potential as a rule-in test. I tested this in a multicentre cohort study of patients with pain and subfertility to assess the accuracy (CA-125) at the newly established cut off value.

A systematic review assessing the reporting of outcomes and outcome measures identified 3 commonly reported outcomes: dysmenorrhoea, dyspareunia and pregnancy. There was heterogeneous outcome reporting across all Randomised control trials (RCT). A systematic review of international and national endometriosis guidelines revealed poor evidence synthesis from treatment effectiveness studies into guideline formation.

A systematic and literature review of treatment effectiveness highlighted significant harms associated with ovarian surgery and oophorectomy.

There is need for further research to develop accurate non-invasive diagnostic tests for endometriosis. The development of a collection of well-defined prioritised clinical

outcomes will augment the usefulness of research to enhance the care for patients with endometriosis.

AIMS / PROGRESS

1. To review the current non-invasive diagnostic strategies for endometriosis
2. To assess the diagnostic accuracy of CA-125 for the detection of histologically confirmed endometriosis
3. To assess the diagnostic accuracy of CA-125 for the detection of endometriosis in a cohort of women with pain or subfertility
4. To assess the relationship between quality of outcomes reported, study quality and journal impact factor in trials of endometriosis
5. To assess the online information available to patients regarding Endometriosis
6. To assess the quality and variation of national and international endometriosis guidelines.
7. To review the risks of surgery for women with endometrioma.
8. To assess the long-term risks of female surgical castration for the management of endometriosis.
9. To assess the role of music in the recovery following endometriosis surgery
10. Discussion

METHODS

- Literature reviews to meet objective 1 & 7
- Systematic review 2,4,5,6,8,9
- Prospective observational study to meet objective 3

RESULTS

1. There is no highly sensitive and specific non-invasive diagnostic marker for endometriosis. The most commonly reported non-invasive diagnostic test was CA-125.
2. 21 Studies met criteria for inclusion. Thirteen studies produced a summary of pooled estimates based on a cut-off value ≥ 30 iu/ml. The sensitivity and specificity of CA-125 ≥ 30 iu/ml for the detection of histologically confirmed endometriosis was 52% (CI 38–66%) and 93% (CI 89–95%).
3. 58 participants with pelvic pain and or subfertility were recruited. Using a pre-defined cut-off value of CA-125 ≥ 30 iu/ml the sensitivity and specificity were 57% (95% CI 37.4 – 74.5%) and 96% (95% CI 81.7 – 99.9%). The area under the curve for positive CA-125 test was 0.85 demonstrating high test accuracy.
4. 54 Randomised controlled trials evaluating surgical interventions for the treatment of endometriosis were identified. These studies reported a total of 164 outcomes using 113 outcome measures. The 3 most commonly reported primary outcomes were dysmenorrhea (10 outcome measures; 23 trials), dyspareunia (11 outcome measures; 21 trials), and pregnancy (3 outcome measures; 26 trials). The median quality of outcome reporting was 3 (interquartile range 4 - 2) and methodological quality 3 (interquartile range 5 - 2). Multivariate linear regression demonstrated a correlation between outcome reporting quality with methodological quality (β=0.325; p=0.038) and year of publication (β=0.067; p=0.040). No relationship was demonstrated between outcome reporting quality with journal impact factor (Rho=0.190; p=0.212) or commercial funding (p=0.370)
5. We identified 750 websites, of which 54 were included in the quantitative analysis. The median values with interquartile ranges are: accuracy 5 (IQR 2 - 8.8); quality 44 (IQR 37.3 - 51); readability 38.2 (IQR 30.7 – 48.0), and credibility 5 (IQR 4 - 7). No website scored highly across all four domains.

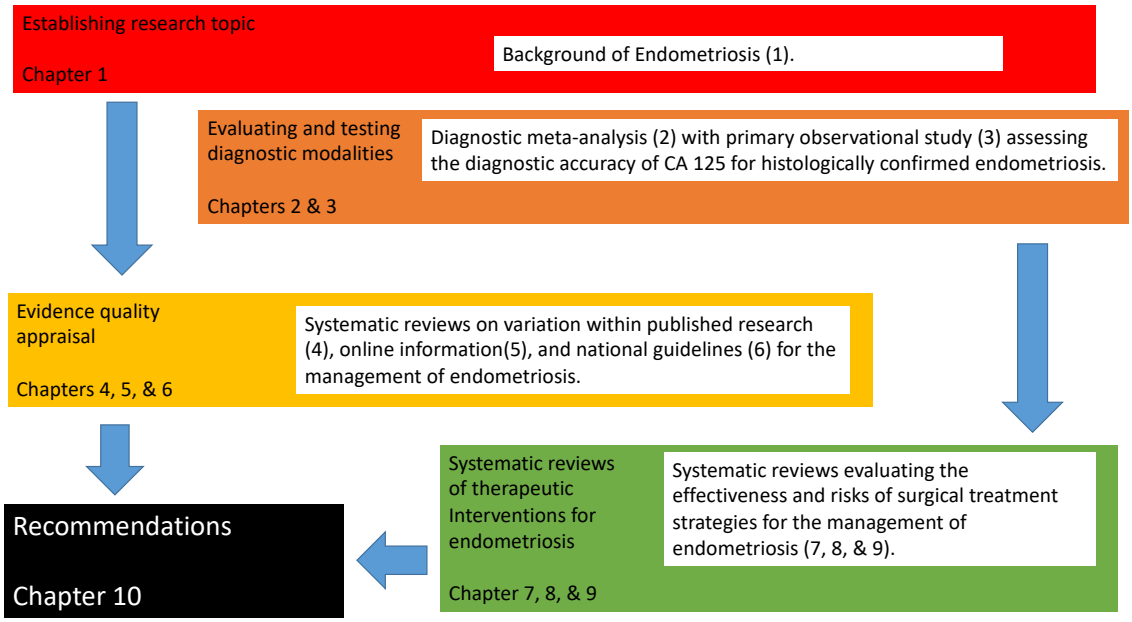
6. We include two international and five national guidelines. No guideline followed the standardised guideline development methods (AGREE-II). Guidelines performed poorly in the domains of stakeholder involvement and rigor of development and very poorly in the domains of applicability and editorial independence. The European Society of Human Reproduction and Embryology (ESHRE) was objectively evaluated as the highest quality guideline (methodological quality score: 88/100). One hundred and fifty-two different recommendations were made, 10 (7%) recommendations were comparable across guidelines.
7. Studies reported the risks of ovarian surgery for future fertility using surrogate markers including: antral follicle count; follicular stimulating hormone; anti-Müllerian hormone (AMH); and dosage of gonadotropins. Surgery for ovarian endometriomas can increase spontaneous conception however, it can also reduce ovarian reserve with increasing numbers of procedures.
8. No studies examined women with endometriosis. The criteria were extended to all benign gynaecological disease. Of 13,470 citations, there were 48 relevant studies (1,272,071 women). Hysterectomy with bilateral oophorectomy (498,603 women) *vs* without (773,468 women) was associated with increase in stroke (RR 1.09, 95% CI 1.03 – 1.16; baseline risk = 35%; number needed to harm [NNH] = 32) and anxiety (RR 1.26, 95% CI 1.06 – 1.51; baseline risk =5.9%; NNH = 65); and decrease in ovarian cancer (RR 0.09, 95% CI 0.04 – 0.19; baseline risk = 2.5%; number needed to treat [NNT] = 44); and breast cancer (hazard ratio 0.85, 95% CI 0.73 – 0.99; baseline risk = 12%; NNT = 55).
9. No studies assessed endometriosis surgery and the criteria was expanded to include all gynaecological surgery. Ten studies were included assessing 1056 participants with size varying between 26 - 372 participants. Choice of music, timing and duration varied. Comparators included routine care, headphones with no music, and recording of operating room noise. Postoperatively music

reduced anxiety (Standard mean Difference (SMD) -0.56 (95% CIs (95%CI) -1.02 to -0.02). There were non-significant improvements in pain SMD -0.37 (95%CI -0.80 to 0.06), and analgesia use SMD -0.32 (95%CI -0.96 to 0.33) and increased patient satisfaction SMD 0.52 (95%CI -0.98 to 2.03), and length of stay (MD -0.19 (95%CI –0.71 to 0.32)).

CONCLUSIONS

1. There is currently no single or multi-tiered, non-invasive, diagnostic test for the detection of endometriosis. CA-125 is the most commonly evaluated marker with limited sensitivity. This has been evaluated against a historic reference standard (visual diagnosis at surgery) associated with significant diagnostic inaccuracy.
2. CA-125 ≥ 30 iu/ml has a high specificity for the detection of histologically confirmed endometriosis. This enables its use as a rule-in test for endometriosis. The sensitivity is poor and a negative test does not exclude disease.
3. Amongst women with pelvic pain and or subfertility in the absence of imaging or historical gynaecological disease, there is a very high positive predictive value for CA-125 ≥ 30 iu/ml. This demonstrates a role for CA-125 as a rule-in test. The sensitivity is poor and a negative test does not exclude disease.
4. There is wide variation in the outcomes reported within endometriosis trials. This prohibits the combination and analysis of results limiting usefulness of research to improve patient care. There is need for a core outcome set within endometriosis trials.

5. Websites providing information for patients typically perform poorly across the domains of quality, accuracy, credibility and readability. Healthcare professionals, and the wider community, should inform women with endometriosis of the risk of outdated, inaccurate, or even dangerous information online.
6. There is substantial variation in the methodological quality of endometriosis guidelines. Future guidelines should be developed with reference to high quality methods, in consultation with key stakeholders including women with endometriosis, ensuring their scope can truly inform clinical practice and eliminate unwarranted and unjustified variation in clinical practice.
7. There are significant risks to ovarian reserve associated with repeated or bilateral ovarian surgery for endometrioma. The decision should be made on a case-by-case basis after fully informed consent with the risks to ovarian reserve being discussed clearly. There is a shift towards performing In Vitro Fertilisation (IVF) without removing ovarian endometrioma amongst women with subfertility.
8. There are significant cardiovascular and psychiatric risks associated with hysterectomy and bilateral oophorectomy compared to hysterectomy alone. The rate of breast and ovarian cancer is reduced.
9. Listening to music following gynaecological surgery offers a significant improvement in pain. There are non-significant improvements in anxiety, satisfaction, and length of stay compared with controls. This is likely to be the case for endometriosis surgery.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Evaluating and testing diagnostic modalities
Chapters 2 & 3
Diagnostic meta-analysis (2) with primary observational study (3) assessing the diagnostic accuracy of CA 125 for histologically confirmed endometriosis.
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PREFACE

This work was conducted during my role as a Clinical Research Fellow at St Bartholomew's Centre for Reproductive Medicine and The Royal London Hospital, Queen Mary University of London between 2013 to 2016.

The Supervisors of the MD study were:

- **Khalid S Khan,** Professor of Clinical Epidemiology and Women's health, Queen Mary, University of London.
- **Dean Nizetic,** Professor of Cellular and Molecular Biology, Blizzard unit, Queen Mary, University of London.

SYNOPSIS

This thesis investigates the diagnostic, therapeutic and methodological challenges faced by clinicians, researchers, and importantly, patients managing endometriosis. It evaluates the diagnostic value of the commonest current non-invasive biomarker marker; CA-125. I assess the impact of intra and post-operative surgical treatment options for the management of endometriosis along with quantifying the quality of current research and information readily available to patients, researchers, and clinicians.

DEDICATION

To my wife, family and inspiration. Motivating me to become a better person every day.

ACKNOWLEDGEMENTS

I feel privileged and honoured to have been given this opportunity by my supervisors; Mr Colin Davis, Professor Khalid Khan, Professor Dean Nizetic and Professor Finbarr Cotter. The support you have provided throughout this academic journey has been invaluable and will never be forgotten.

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A huge thank you to all the consultant Obstetrician Gynaecologists at St Bartholomew's Hospital and The Royal London Hospital for helping me to recruit patients into the study while supporting me between 2013 and 2016.

To those who have provided me with the drive to prove you wrong. I thank you for your words which have inspired me. The lessons I have learned on this journey are more than I could ever have expected and I realise that sources of motivation can come from the most unlikely places.

A loving thanks to my family; Mum, Dad, Joe, and Ben you have supported me and I know will always continue to do so. To my wife, Imogen, who has patiently supported me through this with love and gin.

ABBREVIATIONS

ACCEPT - Australasian Certificate of Reproductive Endocrinology and Infertility Consensus Expert Panel on Trial Evidence

AMH - anti-Müllerian hormone

ACOG - American College of Obstetricians and Gynecologists

AFC - antral follicle count

ART - Assisted reproductive technology

BMD – Bone mineral density

BMI – Body mass index

CA-125 – Cancer Antigen – 125

CDSR - Cochrane Database of Systematic Reviews

CENTRAL - Cochrane Central Register of Controlled Trials

CHM - Chinese Herbal Medicine

CI – Confidence interval

CMR - Cochrane Methodology Register

CNGOF - Collége National des Gynécologues et Obstétriciens Français

COCP – Combined oral contraceptive pill

COH - controlled ovarian hyperstimulation

COMET - Core Outcome Measures in Effectiveness Trials

COX – cycloxgenase

CROWN – CoRe Outcomes in Women's and Newborn health.

CRP – C reactive protein

DARE - Database of Abstracts of Reviews of Effects

DIE - Deep infiltrating endometriosis

EBV – Epstein-Barr Virus

ESHRE - European Society of Human Reproduction and Embryology

FSH - follicle stimulating hormone

GDG – Guideline Development Group

GIFT – Gamete Intra-fallopian tube transfer

GnRHa – Gonadotropin releasing hormone agonist

Hs-CRP - high-sensitivity C-reactive protein

HT – Hormone therapy

HTA - Health Technology Assessment Database

ICSI - Intra-cytoplasmic sperm injection

IELCs - Isolated endometriosis like cells

IL - interleukin

IUI – Intrauterine inseminiation

IUS – Intrauterine system

IVF – In Vitro Fertilisation

LUNA - Laparoscopic Uterosacral Nerve Ablation

MRKH - Mayer-Rokitansky-Kuster-Hauser

MRI – Magnetic resonance imaging

NGG - National German Guideline

NSAID – Non-steroidal anti-inflammatory

ODPHP - Office of Disease Prevention and Health Promotion

OE - Ovarian endometriomata

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO - Prospective Register of Systematic Reviews

PSN - Pre-sacral neurectomy

QUADAS-2 - Quality Assessment of Comparative Diagnostic Accuracy Studies

rAFS – revised American Fertility Society

rAFRM - revised American Fertility and Reproductive Medicine

RCTs – Randomised Controlled Trials

ROC - Receiver operative characteristics

RR – Risk ratio

SD – Standard deviation

SMD – Standard Mean Difference

SOGC - Society of Obstetricians and Gynaecologists of Canada

TCM - Traditional Chinese Medicine

TNFα - Tumour necrosis factor - α

TVOR – Transvaginal Oocyte Retrieval

VAS - Visual analogue score

VEGF - Vascular endothelial growth factor

WES - World Endometriosis Society

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CHAPTER 1:

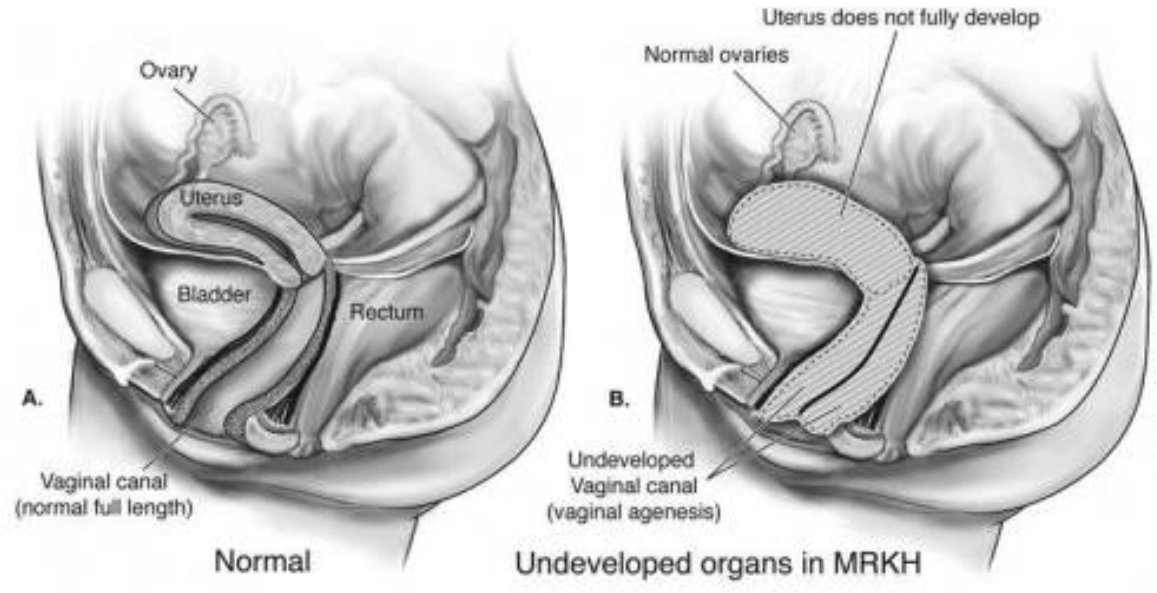
BACKGROUND

1.1 THE HISTORY AND ORIGINS OF ENDOMETRIOSIS

The discovery of endometriosis in 1860 was preceded by the changes brought about by a little known poet turned scientist, Johann Wolfgang von Goethe (1749-1832). This German artist and poet took the principles he learnt in studying works of art and translated these to become principles of science. He was described as observing science through the eye of an artist. His strength in the field of observational science inspired others including Johannes Peter Müller. Müller followed the medical path to become a pathologist and most notably writing and describing the embryological origins of the eponymously named Müllerian ducts and their malformations (1). At the same time Carl von Rokitansky was working in the pathology department of Vienna's largest hospital for Johann Wagner. Rokitansky collected, analysed and correlated pathological observations from the many thousands of autopsies he were to perform over the subsequent two decades. He was the first to accurately describe diseases and their processes, including that of Müllerian agenesis which would over time become known as Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome (Figure 1). The absence of Müllerian tissue was well described when in 1860 Rokitansky were to observe the presence of ectopic Müllerian tissue within the pelvis and the ovaries in association with a normally developed uterus. Rokitansky observed three subtle forms of ectopic Müllerian tissue. The first description is that of lesions invading the myometrial tissue which he named 'Sarcoma adenoids uterinium'. Secondly, he noted that abnormal lesions would invade into endometrial cavity forming a polyp he described 'cystosarcoma adenoids uterinium polyposum'. Finally he described a lesion of Müllerian tissue invasion within the ovary called 'ovarian cystosarcom' (2). His opponents, primarily Von

Recklinghausen, hypothesised that these abnormally sited lesions were merely displaced mesonephric or Wolffian ducts (3).

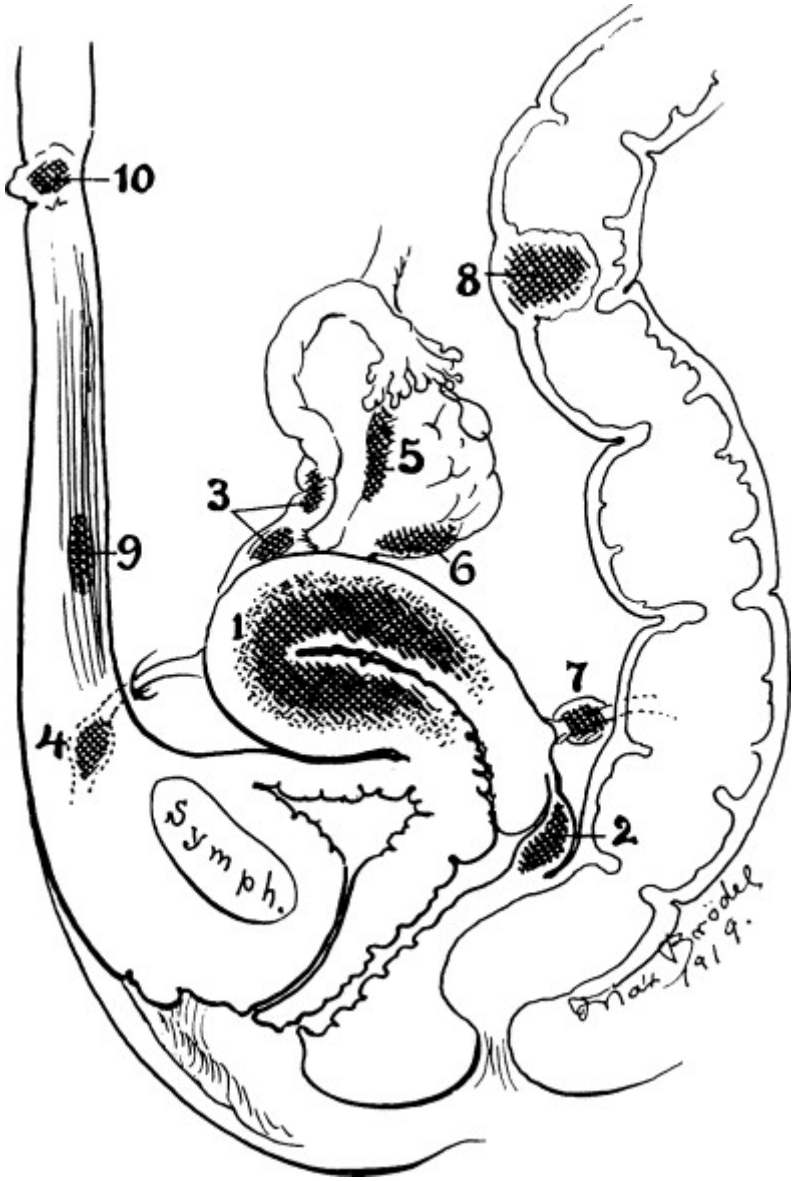
Figure 1 - *Mayer-Rokitansky-Kuster-Hauser syndrome*



It was the surgeon Thomas Stephen Cullen (1868-1953) who noted similarities between the myometrial invasion and those seen in extra-uterine locations such as the recto-vaginal septum, uterosacral ligaments, ovary, bowels, and abdominal wall termed adenomyosis externa. He grouped all these areas of ectopic endometrial cells under the description of adenomyomas (figure 2). In 1923 an established Canadian Gynaecologist John A Sampson observed that during operations timed to occur with menstruation, lesions of the peritoneum would be bleeding similar to that of the shedding eutopic endometrium (4). His initial theories of peritoneal endometriosis surrounded the dissemination of endometrial cells from ruptured endometriomas. However, with closer inspection Sampson hypothesised that endometrial cells refluxed in a retrograde fashion at the time of menstruation developing the now long held theory of causation: retrograde menstruation (5).

Figure 2 *Thomas Stephen Cullen's description of adenomyomas from 1920* **-** *Diagram showing locations of ectopic endometrial tissue (indicated as adenomyomas):*

1, uterine wall; 2, recto-vaginal septum; 3, fallopian tubes; 4, round ligament; 5, hilum of ovary; 6, utero-ovarian ligament; 7, utero-sacral ligament; 8, colon; 9, musculus rectus; 10, umbilicus. From Cullen (6) *with permission.*



With the arrival of laparoscopic surgery in the 1960's onwards, direct visualisation of the pelvis during a chosen cycle stage could be achieved more easily and with less morbidity. The notion that retrograde menstruation only happened to those women suffering from endometriosis was dispelled in 1984 when a study team published

findings that over 90% of women with patent tubes had retrograde menstruation around the time of their menses (7).

The American Fertility Society developed the first quantitative classification system of endometriosis in 1979, this, less than perfect, classification has been revised and incorporated into international standards for describing disease morphology (8). This was followed by a classification system of anomalies of the Müllerian duct (Figure 3).

Figure 3 - Classification of the different anomalies of Müllerian duct development by American Fertility Society (1988) (9)

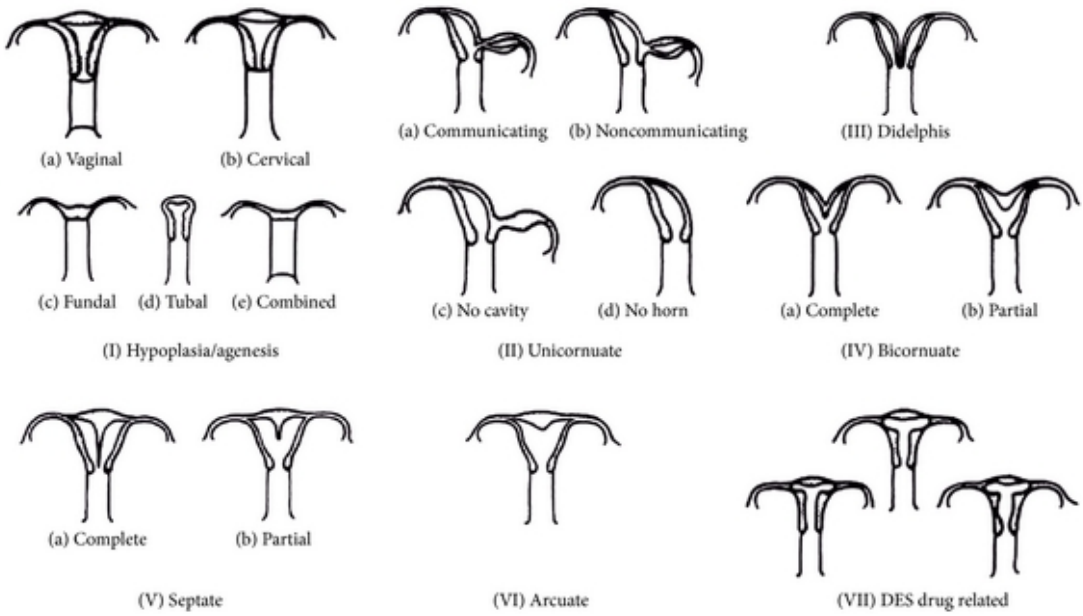
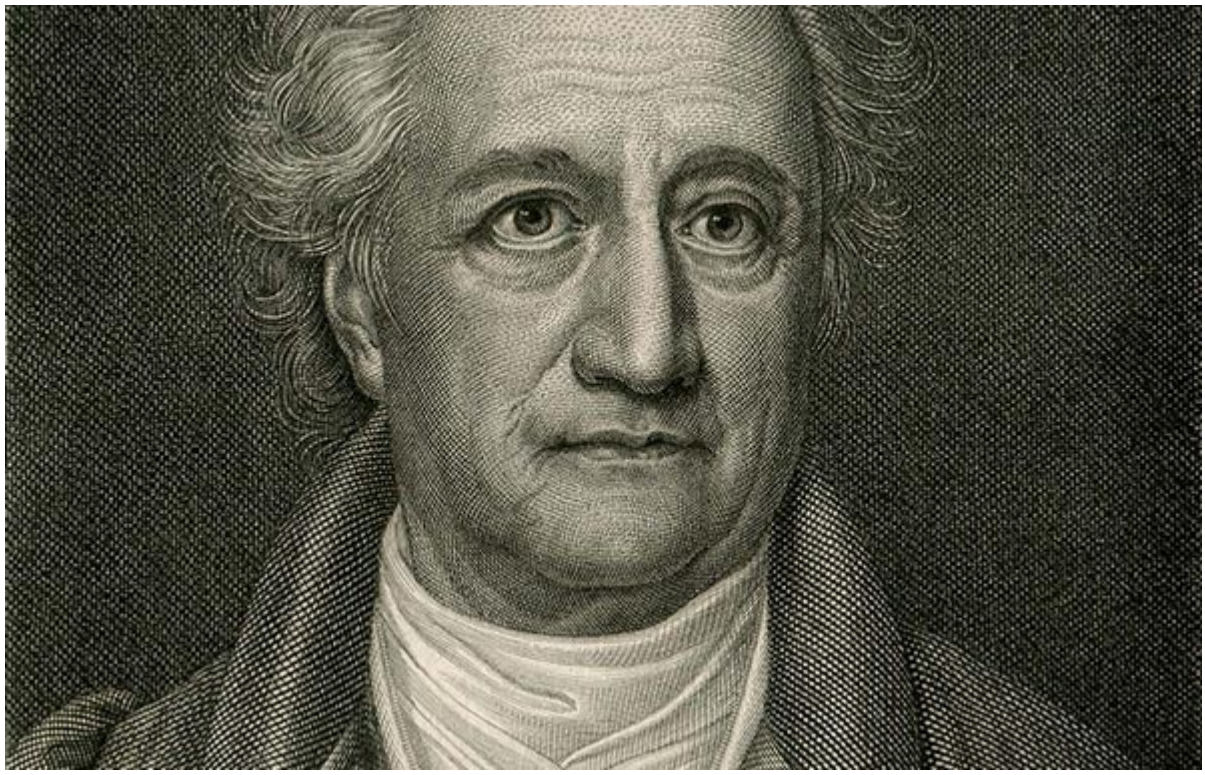


Figure 4 - *Images of aforementioned Scientists*

Johann Wolfgang von Groethe (1749-1832)



Johannes Peter Müller (1801-1858)

Carl von Rokitansky (1804-1878)

Thomas Stephen Cullen (1868-1953)

John A Sampson (1873-1946)

1.2 AETIOLOGY OF ENDOMETRIOSIS

1. Retrograde menstruation
2. Coelomic Metaplasia
3. Immune system dysregulation
4. Life style
5. Familial linkage
6. Endometrial abnormalities
7. Haematological / Lymphatic spread
8. Inflammation

1.2.1 RETROGRADE MENSTRUATION

The original theory proposed by Sampson et al in 1920's describes the reflux of menstrual debris from the uterus backwards through the fallopian tubes and into the peritoneal cavity at the time of a women's menses. This provides a conceptually sound and logical theory as to how cells from the endometrium get to their common sites such as the ovary, the ovarian fossa, the pouch of Douglas, and the uterosacral ligaments. Support for this theory grew with the discovery of higher rates of endometriosis in women with hereditary genital outflow obstruction, iatrogenic outflow obstruction (primates), cervical stenosis and the presence of a uterine septum (10–13). The notion that this only happened to those women suffering from endometriosis was dispelled in 1984 by Halme et al who published findings that over 90% of women with patent tubes had retrograde menstruation around the time of their menses (7).

1.2.2 COELOMIC METAPLASIA

Retrograde menstruation can account for the majority of women diagnosed with endometriosis. There are however a group of men, women and children who fall outside this category. The theory centres on aberrant differentiation of mesothelial cells. Mesothelial cells are simple squamous cells found on cavity linings such as those in the abdomen (peritoneum), brain (arachnoid membrane), and chest (pleura and mediastinum). Under the influence of endogenous or exogenous hormone exposure, mesothelial cells can auto transform into endometrial cells. This has been demonstrated to be the case in in-vitro models (14). Case studies have demonstrated endometriosis deposits in all areas known to contain mesothelial cells such as the peritoneum, the pleural lining of the lungs, the diaphragm, liver, umbilicus and brain (15–20). These theories could be explained through haematogenous or lymphatic spread of endometrial cells while case studies of men presenting with endometriosis following exogenous hormone therapy (HT) or fetuses of female infants with peritoneal endometrial cells adds merit to this theory (21,22).

1.2.3 IMMUNODEFICIENCY

Theories of defective immunodeficiency suggest the survival and development of abnormally located endometrial tissue, in locations such as the rectum or vagina is similar to a foetus evading maternal immunity pathways. This immuno-tolerance in the case of endometriosis allows for reduced menstrual debris recognition and removal providing increased contact time between retrograde menstrual effluent and the pelvic peritoneum (23). There is associated persistence of macrophages noted within the pelvic peritoneum. These macrophages present foreign material including retrograde menstrual effluent to T-lymphocytes for destruction and removal. In patients with endometriosis pro-

inflammatory markers are released disturbing this important balance between macrophages and T-lymphocytes (24). These inflammatory cytokines contribute to ectopic endometrial survival and reduced menstrual debris removal. The resultant environment favours implantation and proliferation of endometrial cells into the lining of the peritoneum and other structures.

1.2.4 LIFE STYLE / ETHNICITY

The prospect of controllable reversible lifestyle choices or exposures affecting the development of endometriosis has been examined. Early epidemiological analysis had thought the disease to be confined to Caucasian women (25) and rare amongst women of African descent (26,27). A more recent and significantly larger longitudinal study of 90,000 American women where those with a diagnosis of endometriosis or infertility were excluded initially revealed that Black African and Hispanic women were 20-40% less likely to go on and get diagnosed with endometriosis than Caucasians. Despite the known linkage between adiposity and oestrogen secretion there appears to be an inverse relationship between weight and risk of endometriosis with patients who have a lower body mass index (BMI) being at greater risk (28). Phenotypical features of ethnicity and life style choices such as hip : waist ration, height or caffeine intake had no relationship with disease prevalence (28). Endometriosis was historically termed “the disease of the rich” (29) but recent studies have failed to address this variable (30).

1.2.5 FAMILIAL LINKAGE

Endometriosis has been shown to have a high degree of hereditability since it was first investigated in 1970 (31). Numerous subsequent twin and family studies have

demonstrated a 5 to 7-fold increase risk in an individual with a family history of the disease (32–34). Two small twin studies of mono-zygotic twins with one twin affected by endometriosis demonstrated a 75-87% concordance rate (35,36). A large Genome Wide Association study evaluation of single-nucleotide polymorphism has highlighted an association between a gene (WNT4) located on chromosome 1. WNT4 is important for steroidogenesis, ovarian follicle development and the natural development of the female reproductive tract and a very plausible candidate for endometriosis based on its biological functions (37).

1.2.6 ENDOMETRIAL ABNORMALITIES

The endometrium is a complex structure that changes throughout a normal menstrual cycle under the influence of circulating hormones. The role of apoptosis in normal endometrium is to eliminate senescent or dysfunctional cells, as a way for tissue repair at each menstrual cycle. Apoptosis is a fundamental physiological process that allows the body to maintain homeostasis by eliminating dysfunctional cells. In women with endometriosis, endometrial cells regurgitated into the peritoneal cavity lack the appropriate mechanisms of programmed cell death and can therefore escape clearance and survive to invade pelvic structures through concomitant overexpression of anti-apoptotic factors and reduced expression of pro-apoptotic factors (38,39).

1.2.7 HAEMATOLOGICAL / LYMPHATIC SPREAD

Endometriosis has been found during histopathological examination of pericolic lymph nodes removed during bowel surgery for endometriosis (40,41). Further studies have found the prevalence of isolated endometriosis like cells (IELCs) in pelvic sentinel lymph

nodes in 11% of women with ovarian or peritoneal endometriosis (42). Recent studies using cell filtering technology, commonly used for the detection of circulating tumour cells, have demonstrated the presence of peripherally circulating serum endometrial like cells (43).

1.2.8 INFLAMMATION

Inflammation is believed to play a fundamental role in the development and progression of endometriosis(44,45).

Endometriotic tissue, unlike endometrial tissue, is associated with the overproduction of inflammatory markers; prostaglandins, metalloproteinases, cytokines, and chemokines (46–49). Overexpression of prostaglandin E2 in endometriotic tissue is sustained by overexpression of cyclooxygenase (COX) 2 and CYP19A1. Prostaglandin E2 released following the inflammatory response stimulates the expression of all steroidogenic genes necessary to enable the endometriotic stromal cell to synthesise estradiol from cholesterol (50). Oestrogen enhances the survival or persistence of endometriotic tissue, prostaglandins and cytokines mediate pain, inflammation, and infertility (51,52).

Pro-inflammatory cytokines such as tumour necrosis factor α (TNFα) and IL-1b initiate the development and progression of endometriosis via: pleiotropic, cytostatic, chemoattractant, or angiogenic effects (53). The presence of peritoneal TNFα and serum levels of Inter-Leukin-1b have been associated with endometriosis suffers (54), dysmenorrhoea (55), and severe endometriosis (45).

The inflammatory process of oxidative stress occurs when there is an imbalance between reactive oxygen species (ROS) production and the antioxidant defence (56). Oxidative stress has been associated with several chronic inflammatory diseases including endometriosis (44). As a result, ROS promote the growth and adhesion of

endometrial cells within the peritoneal cavity, leading to disease establishment and symptoms of pain and infertility (57,58).

1.3.1 DISEASE CLASSIFICATION

Since endometriosis was first recognised, a classification has been necessary to describe this disease. Early classification scores were based on locality of the disease and had little correlation with disease severity or the clinical manifestations. Initial attempts to produce a classification scale for the disease originated with Sampson et al in 1921 (59) and followed some years later by Albrecht et al (60). Acosta et al (61) were the first group to link the disease severity and clinical pregnancy rates. The use of classification tools in Endometriosis has become widespread and unified since the revised American Fertility Society published their points based score system in 1986 following its original publication in 1979 (8,62) This established classification tool, is not without its limitations and was again revised and renamed in 1996 to form the revised American Fertility and Reproductive Medicine (rAFRM) score (63).

The disease has had 5 classification tools, the revised American Fertility Society (rAFS), Buttram, Kistner, Acousta and Enzian classification method. The rAFS is widely used, in comparison to the Enzian classification which is limited to German speaking countries. The remaining classification systems have had historic use and are no longer widely accepted.

The purpose of a classification system is to provide a reproducible set of symptom or prognostic markers that can be accurately translated to patients. The classification and diagnosis of the disease should be simple and accurate regardless of clinician and country.

The difficulties of producing a classification system for endometriosis are numerous. The visual appearance of lesions varies widely resulting in significant intra-observer and

inter-observer variability. There is up to 50% false positive rate with visual diagnosis of endometriosis given its varied appearances (64). The revised American Society Classification tool will be used during this thesis.

1.3.2 REVISED AMERICAN FERTILITY SOCIETY CLASSIFICATION (RAFS)

The American Fertility and Reproductive Medicine society's classification tool is used most widely for both clinical and academic practice. Values are assigned to endometriotic lesions of the ovary and peritoneum according to size and depth of infiltration, either superficial or deep. Additionally, points are awarded for adhesions on the fallopian tubes and ovary along with partial or complete obliteration of the posterior cul-de-sac. After a full assessment the points are totalled to provide an overall score, staging and lay description; 1-5 Stage 1 (minimal), 6-15 Stage 2 (mild), 16-40 Stage 3 (moderate), >40 stage 4 (severe) (Figure 5)

Figure 5 – *The revised American Fertility Society Classification*

THE AMERICAN FERTILITY SOCIETY REVISED CLASSIFICATION OF ENDOMETRIOSIS

Patient's Name _____ Date _____

Stage I (Minimal) - 1-5
Stage II (Mild) - 6-15
Stage III (Moderate) - 16-40
Stage IV (Severe) - >40
Total _____

Laparoscopy _____ Laparotomy _____ Photography _____
Recommended Treatment _____
_____
Prognosis _____

PERITONEUM	**ENDOMETRIOSIS**	<1cm	1-3cm	>3cm
	Superficial	1	2	4
	Deep	2	4	6
OVARY	R Superficial	1	2	4
	Deep	4	16	20
	L Superficial	1	2	4
	Deep	4	16	20

	POSTERIOR CULDESAC OBLITERATION	Partial	Complete
		4	40

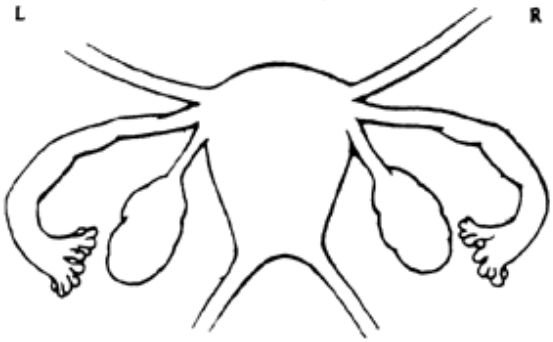
OVARY	**ADHESIONS**	<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
	R Filmy	1	2	4
	Dense	4	8	16
	L Filmy	1	2	4
	Dense	4	8	16
TUBE	R Filmy	1	2	4
	Dense	4*	8*	16
	L Filmy	1	2	4
	Dense	4*	8*	16

*If the fimbriated end of the fallopian tube is completely enclosed, change the point assignment to 16.

Additional Endometriosis: _____

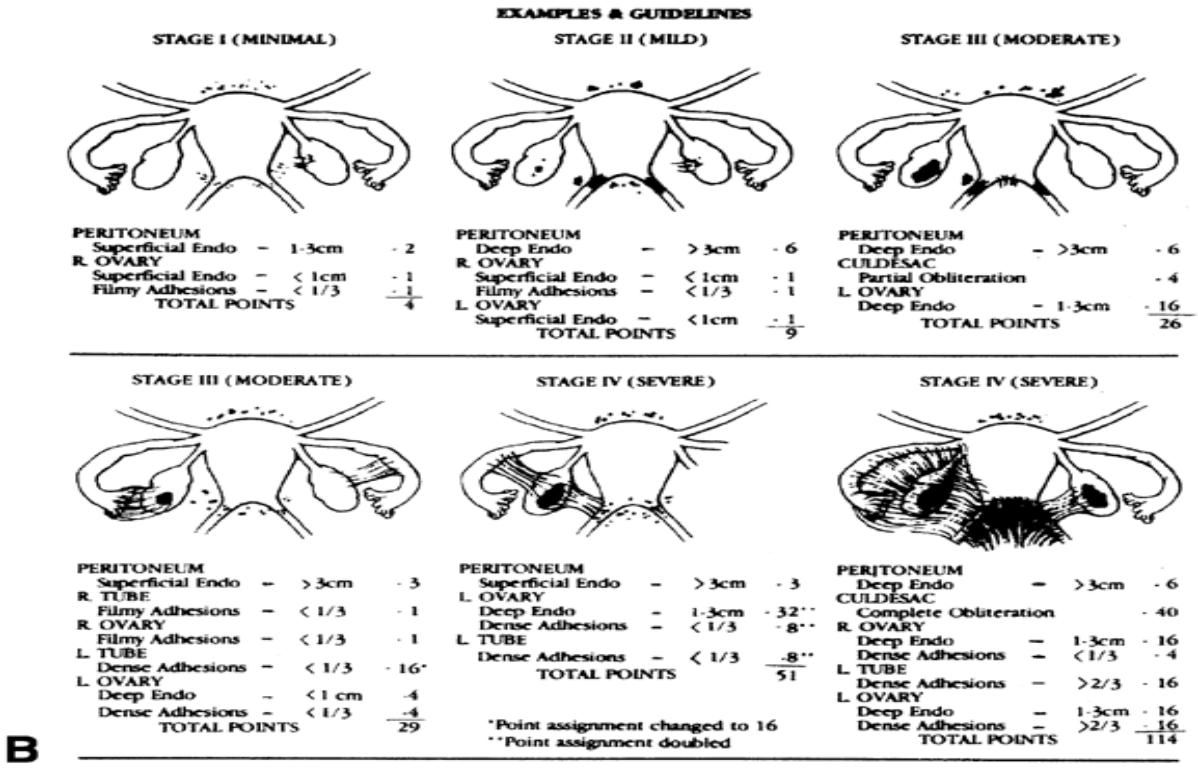
Associated Pathology: _____

To Be Used with Normal Tubes and Ovaries



To Be Used with Abnormal Tubes and/or Ovaries

A



This scale has many advantages. It the most widely used and validated assessment tool available. The simplistic scoring system used provides ease of use for the clinician and an uncomplicated lay description available to the patient.

Limitations

This classification has limitations and the scoring system does not account for the disease morphology or its penetration to surrounding structures. The numerous points available for lesion size reduces the reliability of its reproducibility with intraobserver and interobserver reliability accounting for a change in the disease score in 38% and 52% of patients respectively. The score ranges from 0-90 and greatest intraobserver and interobserver variability was seen in ovarian endometriosis and endometriosis effecting the posterior cul-du-sac (65).

With the exception of invasive disease the rAFS correlates poorly with, fertility (66,67), dysmenorrhea, dyspareunia, and pelvic pain (68). It is because of this poor association

with rAFRM score and fertility that Adamson and Pasta developed the Endometriosis Fertility Index (69) which includes clinical information on fertility and sterility.

1.4 ENDOMETRIOSIS SYMPTOMS

1.4.1 PAIN

Endometriosis can be associated with a variety of different pain symptoms without correlation to disease severity (70,71). These symptoms include dysmenorrhoea, dyspareunia, dyschezia, dysuria, and chronic pelvic pain (71). The precise aetiological origins of endometriosis associated pain remain poorly understood. Theories include: 1) bleeding from active endometriosis lesions, 2) release of pro-inflammatory markers from the endometriosis lesions, and 3) direct invasion or irritation of the pelvic peritoneal nerves (72). Pain is both subjective and difficult to measure. Pelvic pain is not diagnostic of endometriosis and there are no associated patterns of pain presentation that can be accurately linked to the disease making the decision for laparoscopic investigation difficult. Pain mapping of those women with and without endometriosis suggest that symptoms of chronic pelvic pain, dyschezia, and dyspareunia were much more likely to be reported amongst women with endometriosis than without (73).

1.4.2 INFERTILITY

Endometriosis is increased amongst women with infertility. The disease prevalence is believed to be up to 50% of infertile women(74). Estimates suggest around 50% of women with surgically confirmed endometriosis will not achieve a spontaneous pregnancy (69,75–77). The monthly fecundity rate is significantly less for those with confirmed endometriosis (2-10%) compared to those fertile couples (78).

Large retrospective analyses have shown non-significant differences in IVF outcomes between those women with endometriosis to either tubal factor controls or all other

causes (79,80). The concerns that IVF may prompt a deterioration in endometriosis symptoms or disease progression has not been demonstrated (81).

1.4.3 QUALITY OF LIFE

Quality of life is affected in a complex way by each individuals' physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationship to salient features of their environment (82).

In addition to physical symptoms, women with endometriosis have a higher prevalence of non-physical symptoms such as depression (83,84). Many different studies have aimed to assess quality of life but have had limited validity owing to low study size, poorly selected controls or non-validated assessment tools (85–87). Recently validated assessment tools include the Short Form 36, a questionnaire designed to measure the impact of endometriosis on quality of life research(88).

Psychological quality of life in 479 endometriosis patients was significantly reduced compared to patients with serious chronic diseases such as cancer (89).

1.5 DIAGNOSIS

1.5.1 Background

1.5.2 Current guidance

1.5.3 Blood markers

1.5.4 Endometrial markers

1.5.5 Urinary markers

1.5.6 Clinical symptom prediction models

1.5.7 Imaging prediction

1.5.8 Conclusions

1.5.1 BACKGROUND

Endometriosis is a varied and enigmatic disease. It is histologically characterised by the presence of ectopic endometrial glands and stroma distant to the uterus. Common sites include the pelvic organs and the peritoneum surrounding the uterus (90). Endometriosis is a chronic benign oestrogen-dependent disease affecting 10% of women during their reproductive years (91). The prevalence increases to 35–50% amongst women with pelvic pain and or subfertility (25,92–94). Endometriosis is often undiagnosed, and average delays from symptom onset to diagnosis are 6–11 years (95–97). Endometriosis is characterised clinically by noncyclical pelvic pain, dysmenorrhoea, dyspareunia and subfertility (71,98–100). The disease has estimated annual costs of 9579 Euro per patient, comprising one-third of the direct healthcare costs with two-thirds attributed to loss of productivity (101). The disease manifests itself in three distinct visually and pathological forms: superficial peritoneal, ovarian endometrioma and DIE. There is significant heterogeneity between these three disease forms and debate is ongoing whether despite their similar histopathological appearance they are in fact separate processes (102). The surgical findings are widely classified according to the revised American Fertility Society (rAFS) despite this having very poor correlation with postoperative outcomes, symptomatology and high intra-user variability (103–105). The development of a screening test for endometriosis relies on several critical properties

including high specificity, high sensitivity, reproducibility simplicity and patient acceptability or minimal invasiveness. A marker or test must provide consistent results among a varied geographical and ethnically varied population. This marker or test has not been able to meet these criteria nor has it been validated and as a result this has been highlighted as an endometriosis research priority (106).

1.5.2 CURRENT GUIDANCE

To date, we have been unable to accurately predict the presence of endometriosis with symptom, clinical, blood, urine nor image-based screening tests. The combination of laparoscopy and histopathological confirmation is currently the gold standard for diagnostic confirmation of endometriosis (107). Endometriosis has a myriad of macroscopic appearances that can lead to false-negative and false-positive diagnosis via visualisation alone (108). This is more evident in peritoneal endometriosis than ovarian and DIE; nonetheless, the visual diagnosis of endometriosis has been demonstrated to be unreliable (64,109). The European Society of Human Reproduction and Embryology (ESHRE) committee of endometriosis experts set up a guideline development group that stated visually confirmed endometriosis at laparoscopy is of limited value without a biopsy confirming histological presence (90) . A study supporting this excised 122 visually confirmed endometriosis lesions from 54 patients and found that only 54% of these lesions were histopathologically confirmed endometriosis (110). This limited diagnostic accuracy of visualisation was compounded by a meta-analysis of studies demonstrating close to 50% misdiagnosis in rAFS stage I–II with visualisation alone (64). The combination of poor diagnostic accuracy and poor prognostic capabilities of disease presence and quantity makes for challenging consultations with patients when discussing the management of the disease.

There is consensus in the World Endometriosis Society (WES) that the development of a reliable non-invasive test is one of the top research priorities in endometriosis (106,111). The development of biomarker test for the detection of any disease is long, difficult and riddled with uncertainty. The development can be broadly broken down 4 phases:

1) Pre-clinical discovery phase: preclinical studies identifying potential biomarkers
2) Retrospective Validation: those known to have the disease are tested to assess the accuracy in a preclinical setting.
3) Prospective validation: this establishes the diagnostic accuracy and both positive and negative predictive value.
4) Commercialisation: industry development of the test for widespread distribution.

The development and implementation of a reliable non-invasive test for endometriosis will have a profound impact on reducing the health care burden, current costs (112) while improving the quality of life for an estimate 10% of the female reproductive population (101,113,114).

1.5.3 BLOOD MARKERS

The chronic inflammatory nature of endometriosis further challenges the specificity of tests based on mediators of inflammation. The most commonly used biomarker for preoperative assessment is CA-125 (CA-125). This is a glycoprotein found within the cells lining the female genital tract and is raised in both epithelial ovarian cancer and other gynaecological diseases (115–117). This was systematically reviewed with a meta-analysis finding insignificant sensitivities and specificities to justify its use as a predictive marker (116) though serum levels appear to rise with increasing disease severity (118). CA-125 along with other glycoproteins has been analysed by research teams in Leuven who have kept a bank of frozen blood samples from patients since 1999. The team were able to demonstrate the accuracy of CA-125 with sensitivity and specificity of 78 and 51% (119). There are significant data to suggest that CA-125 has a limited role in the assessment and follow-up of endometriosis (120) with limited studies suggesting that vascular endothelial growth factor (VEGF) could potentially provide a more accurate means of diagnosis with sensitivities and specificities of 93.3 and 96.7%, respectively (121). There are limited studies including diagnostic data to support the use of VEGF

hence this thesis explored the use of CA125.

Inflammatory markers such as IL-8 [44] and high-sensitivity C-reactive protein (hs-CRP) (122) have been analysed in large studies. The use of CRP in the detection of many inflammatory conditions is widely recognised, yet its use in endometriosis is uncertain. Previous studies have demonstrated hs-CRP as a more useful marker than CRP but without conclusively demonstrating its use as a marker in its own right (123–126). Thubert et al. (122) examined the significance of hs-CRP in 370 women with histopathological confirmed endometriosis compared with those patients (n.464) who had had negative laparoscopies. Over a study period of 4 years, the authors demonstrated no significant difference in this marker between the case and control group (122).

Endometriosis is widely considered an inflammatory process of unclear aetiology. The inflammation pathway is associated with oxidative stress (127) which results in the production of free radicals and reactive oxygen species (127). When these by products are not adequately metabolised and removed, they may cause oxidative alteration in proteins, lipids, carbohydrates, nucleic acids and their sequential signalling pathways. This cascade of events that follows oxidative stress requires several key components including thiols and carbonyls that have become the focus of biomarker analysis (128) and have been linked to endometriosis and subfertility (44,56). In the quantitative analysis of serum thiols in 67 cases of histologically confirmed endometriosis compared with 41 controls, quantitative analysis demonstrated significantly lower levels of thiols and carbonyls amongst endometriosis cases compared with controls. Receiver operating curve analysis provided cut-off levels at 396.44mM and 14.9 mM for thiols and carbonyls, respectively, and sensitivity of 73.1% and specificity of 80.5% for thiols and 94 and 51.2% with carbonyls (129). This finding was contradicted by several studies demonstrating no association between endometriosis and markers of oxidative stress (130,131). More recent areas of biomarker development have included micro RNAs (miRNAs). These circulating lengths of 19–25 nucleotides have been demonstrated to

influence mRNA translation and degradation resulting in a sequential impact on gene and proteomic expression (132–134). The aberrant expression of miRNA has been linked to chronic diseases including endometriosis [60]. Variation between miRNA levels in eutopic and ectopic endometrium of controls and those patients with endometriosis has led to further analysis of serum miRNA profiles (135–138). A quantitative analysis of miRNA levels in women with stage III–IV endometriosis demonstrated high levels of accuracy with sensitivities and specificities up to 90% for miRNA-17- 5p, miRNA-20a, miRNA-22 (139). This contrasts to Suryawanshi et al. (140) who found differentiation between endometriosis patients and controls with miRNA-16, miRNA-191 and miRNA-195 at sensitivity and specificity of 88 and 60%, respectively. The most promising study yet from Wang et al. (141) compared 60 patients with histopathological confirmed endometriosis to 25 patients with a negative laparoscopy. This study found discriminatory sensitivities and specificities of 93.2 and 96% when combining miR-199a, miR-122, miR-542-3p and miR-145. We were unable to combine this data for meta-analysis due to the multitude of different miRNA markers evaluated, however, this field of endometriosis research appears to be a growing area of interest.

1.5.4 ENDOMETRIAL MARKERS

The hormonal variation in ovulatory women throughout their menstrual cycle results in endometrial molecular signature change depending on the stage in the cycle. This presents a significant challenge with regard to endometrial-based biomarker development. Although a cycle phase specific test may be acceptable to optimise sensitivities and specificities, this may not be practical with women having irregular menstrual cycles. This is particularly relevant in studies analysing eutopic mRNA expression (142).

Recent studies have found that aberrant neuronal growth may contribute to abnormal fertility and uterine disorders including endometriosis. The hypothesis that increased

neuronal innervation to endometrial cells (eutopic and ectopic) could be reflected in an endometrial biopsy to detect a neuronal protein called protein gene product 9.5. The association between protein gene product 9.5 in the functional layer of the endometrium and the presence of endometriosis in the pelvis has, like many markers, shown promise (142–148). This C-terminal hydrolase dissociates ubiquitin peptide bonds and thus regulates proteolysis (149). The use of this semi-invasive biomarker has sensitivities ranging from 80 to 81% with specificity 92–100% and did not appear to vary by phase of the menstrual cycle (148,150). Protein expression correlated with the presence of endometriosis, whereas the gene expression did not; this discordance between genomic expression and proteomic expression suggests that expression of these proteins is influenced by mechanisms taking place in the post-transcription period (150). We chose not to perform a meta-analysis as this was being performed by the Cochrane gynaecology and fertility group (151).

1.5.5 URINARY MARKERS

In a recent evaluation of urinary proteomics amongst 11 women with endometriosis and 6 women without, cytokeratin 19 (CK19) was found to be significantly upregulated amongst those women with endometriosis (152). The authors of this scoping study detected 917 protein spots of which 130 were statistically significant with urinary cytokeratin 19 as the most accurate of urinary protein markers for endometriosis (152). The authors did not set out to test this specific biomarker and little is known about the role of CK19 in endometriosis. Further studies have continued to demonstrate a high specificity (94%) but a low sensitivity (11%) in a population of 98 women with pelvic pain. In the group which had a negative index test (CK19), 56 of the 89 (62%) were found to have histologically confirmed endometriosis compared with two patients from nine who had a false-positive result exposing many women to unnecessary interventions (153). A Study of Chinese women undergoing gynaecological investigation examined the role of urinary proteomic expression as a screening tool. The significance of urinary angiogenic

markers and cytokines has previously been demonstrated in both systemic and urogenital diseases such as nephrotic syndrome, hypertension and cardiac failure (154–158). ELISA analysis of creatinine-adjusted urinary vitamin-D binding protein for 57 women with endometriosis compared with control group of 38 women without endometriosis produced a sensitivity of 58% and specificity of 76% (159). A diagnostic review performed by Cochrane subfertility and menstrual disorders group revealed only 8 eligible studies concluding that there is insufficient evidence to recommend a urinary biomarker for use in the diagnosis of endometriosis (160).

1.5.6 CLINICAL SYMPTOM PREDICTION MODELS

Endometriosis is known for a triad of pain symptoms: dysmenorrhoea, dyspareunia and pelvic pain; however, multiple symptom-based predictive tools have failed to accurately predict endometriosis from those without endometriosis. A detailed pelvic examination has previously been unable to accurately predict the presence of endometriosis as many women have normal findings (161,162). The ill-defined relationship between clinical stage (rAFS) and symptom severity provides clinicians with further challenges. Several systematic reviews and studies of endometriosis have attempted to develop predictive analysis with a combination of examination, symptoms and ultrasound to add diagnostic accuracy to tools which are individually imprecise (163–165). Despite the low individual clinical accuracy, pelvic examination remains a crucial component to the preoperative assessment.

1.5.7 IMAGING PREDICTION

Imaging modalities have a major role in the investigation and diagnosis of gynaecological disease. Ultrasound alone provides high sensitivities of up to 97% in stage three or four

endometriosis but consistently low sensitivities of 10% in stage I & II endometriosis. This demonstrates an ability for a positive scan result to diagnose the disease but not exclude the disease when it is negative (166). Ultrasound imaging has a historic use in identifying ovarian endometrioma. The diagnosis of endometrioma with ultrasound has moderate sensitivities but high specificities, using three commonly reported ultrasound signs: ground glass appearance, septations 1–4, papillaries without blood flow. When premenopausal status is added, the sensitivities range from 62 to 73%. The experience and subjective assessment of a senior trained sonographer increases sensitivities to 81% (167,168). Endometriosis is a disease characterised by inflammation and fibrosis more commonly causing adhesions rather than ovarian endometrioma (169). Several ultrasound studies have tried to address this as a potential area for non-invasive diagnosis. Adhesions are not well visualised on ultrasound and in the absence of endometriosis or other inflammatory processes, the uterus and ovaries can move freely. However, when endometriosis is coexistent, adhesions commonly form between the ovary and the uterus increasing in frequency and severity with advancing disease preventing this movement (170). Several studies have looked to assess the diagnostic accuracy of adhesions or pelvic immobility at ultrasound to predict endometriosis presence at surgery (171–174). The diagnostic accuracies are variable with a potential use in the diagnosis of deep infiltrating disease, pouch of Douglas obliteration (173,174) and ovarian adhesions. MRI is now more commonly used in the preoperative setting for women with known or suspected endometriosis. This modality is not effective in detecting superficial endometriosis but more beneficial in assessing moderate to severe disease stages III–IV. The ability for MRI to diagnose endometriosis depends on the stromal to glandular consistency of the lesion, the extent of haemorrhage and inflammatory response (175). Haemorrhage within the ovary is a key feature of endometriomas and MRI is commonly used to assess complex ovarian cysts found during ultrasound in which a diagnosis is not certain. This has been shown to have high specificities of 92% but lower sensitivities of 67%, suggesting alternative pathologies share similar MRI characteristics (176). The preoperative assessment and diagnosis of

endometriosis stage III–IV is crucial for surgical planning to minimise the risk of complications in moderate to severe disease (177). The identification of solid endometriotic nodules together with adhesions is well documented with MRI. In those lesions with pure fibrous components, images will elicit low signal intensity with T-1 and T-2-weighted images, whereas those with a heavy glandular component demonstrate high signal intensity with T-1 and T-2- weighted images. The commonest lesions found are a mixture of fibrous and glandular endometriosis but with stromal/fibrous predominance. These demonstrate low signal attenuation from the fibrous element, irregular speculated edges and cystic components with internal high signal intensity from areas of haemorrhage on T-1 images (178,179). The specificities appeared to be consistently high (176,179–181), whereas sensitivities varied from 23% to 100% (179,182,183) depending on the location of endometriosis deposit. The commonest location for DIE to be found was the recto–cervical junction with high sensitivities (95%) and specificities (100%). We chose not to combine biomarkers with imaging as this has been the subject of several previous studies evaluating the use of ultrasound or MRI with biomarkers to improve diagnostic accuracy (184–190).

1.5.8 CONCLUSION

The non-invasive diagnosis of endometriosis remains a challenge for both patients and healthcare professionals. The annual healthcare costs are comparable to diabetes for this chronic disease affecting 10% of the female reproductive population (101). With the average age of first live birth increasing (191), it is likely that gynaecologists we will see an increase in disease progression and symptomatic patients. This will have an associated increase in health economic costs from surgery and fertility treatments unless accurate non-invasive diagnostic tests are developed. The development of a robust non-invasive test for endometriosis is of great clinical importance (106), yet it has many inherent difficulties related to cyclical hormonal fluctuations. The pathway that leads from a theory to the development of a diagnostic test is long, complicated and difficult (192). Further understanding of the aetiology and basic science processes involved in the development of this disease will aid in the development of a non-invasive test. The commonest biomarker that has been evaluated is serum CA-125. Previous studies have been meta-analysed demonstrating poor sensitivity and moderate specificity. This was performed over ten years ago with a historic reference standard (visual diagnosis). There is need for re-evaluation of the accuracy of CA-125 for the diagnosis of histologically confirmed endometriosis.

This section (1.5) of Chapter 1 was based on the following publication:

Preoperative assessment and diagnosis of endometriosis: are we any closer?

Hirsch M, Davis CJ.

Curr Opin Obstet Gynecol. 2015 Aug;27(4):284-90.

1.6 ENDOMETRIOSIS TREATMENTS

1.6.1 MEDICAL TREATMENTS

ANALGESIA

Non-Steroidal Anti-Inflammatory drugs (NSAIDs) are a common initial treatment modality for women presenting to their doctor with symptoms suggestive of endometriosis. However, there is minimal evidence for the use of NSAIDs as analgesia for endometriosis related pain (193).

HORMONAL TREATMENTS FOR PAIN

LEVONORGESTREL RELEASING INTRA-UTERINE SYSTEM (IUS)

The Trade name Mirena is a drug releasing intra-uterine system (IUS) which secretes 20 mcg Levonorgestrel from the coil into the uterine cavity every 24 hours. The synthetic progestogens have local effects on the surrounding tissue (endometrium) causing suppression of endometrial thickening, reduced menstrual loss, and reduced endometriosis associated pain (194–196). There are other levonorgestrel releasing systems available without the evidence base to support their use in the treatment of endometriosis associated pain.

OVULATION SUPPRESSION

COMBINED ORAL CONTRACEPTIVE PILL (COCP)

The use of the combined oral contraceptive pill (COCP) is widely considered a first line of treatment for a patient with suspected endometriosis related pain. They act by inhibiting ovulation and reducing the risk of endometrioma formation (197), inducing atrophy of endometriosis, enhance apoptosis of endometriotic tissue and reduce growth/spread of the disease (198,199). The post-operative use of the COCP leads to an 80% risk reduction of endometrioma recurrence and dysmenorrhoea (200–203).

GONADAOTROPIN RELEASING HORMONE AGONISTS (GNRHA)

The use of Gonadotrophin releasing hormone agonists (GnRHa) is common for the treatment of endometriosis. This treatment causes central pituitary down regulation following repeated agonist stimulation inhibiting the production of ovarian hormones essential for the development, maintenance and progression of endometriosis. The use of GnRHa has been shown to reduce pain and recurrence of endometriosis (204–206). If a GnRHa is chosen, add-back HRT is recommended to prevent bone loss and hypoestrogenic side effects. Add back HRT therapy is not known to affect the treatment efficacy of GnRHa (207–210). The use of HRT is recommended to be continuous and combined as unopposed oestrogen therapy is believed to carry a greater risk of endometriosis symptom recurrence. There is limited high quality evidence to support this treatment recommendation. Comparisons of continuous combined HRT have demonstrated the symptom recurrence risk is lowest with Tibolone, a synthetic HRT (107,211).

PROGESTOGENS

The use of progestogens is believed to induce decidualisation and atrophy of lesions. It was the observation of improved clinical symptoms during pregnancy that led to the evaluation of progestogens in the medical treatment of endometriosis associated pain (212,213).

ORAL PROGESTOGENS

Several small randomised control trials have evaluated the efficacy of oral progestogens. These small studies have shown non-significant benefits compared to placebo in the outcomes of: change in pain at 12 months and AFS score. There were significant improvements demonstrated in: pelvic pain and sum of all symptoms at both six and twelve months when compared to placebo but these were not seen when compared to other treatments. There were significantly greater patient reported in efficacy of treatment associated with other treatments when compared to oral progestogens (214).

INJECTABLE PROGESTOGENS

The use of depot progestogens is associated with significant improvement in dysmenorrhoea at 6 months. The use of injectable progestogens compared to other treatments is associated with significant increase in adverse effects, including: injection site reactions, bloating, intermentrual bleedings, weight gain, amenorrhoea, and nausea (214).

PROGESTOGEN IMPLANTS

The use of implantable progestogens for the treatment of endometriosis associated pain has undergone limited evaluation. A single non-inferiority randomized control trial has found implantable progestogens to be non-inferior to levonorgestrel releasing intra-uterine system in pelvic pain, dysmenorrhoea, and quality of life (215).

1.6.2 ALTERNATIVE TREATMENTS

ACUPUNCTURE

Acupuncture is a very commonly used form of Traditional Chinese Medicine (TCM) which has been practiced for over a thousand years (216). Western culture has increasingly adopted this form treatment since the start of the twentieth century. The single randomised controlled trial included in analysis by Cochrane reviewers found that auricular acupuncture significantly reduced severe dysmenorrhoea compared to a separate TCM (217).

CHINESE MEDICINE

Chinese Herbal Medicine (CHM) has traditional use dating back over 2000 years. Chinese medical theories believe the symptoms of pain associated with endometriosis originate from stagnation in the blood leading to a blockade in the blood flow to an area and subsequent pain. The hypothesised mechanism of action for CHM for endometriosis centres on the regulation of endocrine, immunological, circulatory and inflammatory pathways (218,219).

Two RCTs exist comparing the use CHM with western medicine. CHM demostrated improvement when compared to danazol use for the treatment of dysmenorrhoea, adenexal mass shrinkage, vaginal nodularity, lumbosacral pain and rectal pain but no significant differences in reduction of dysmenorrhoea nor pregnancy rate against gestrinone (220).

1.6.3 SURGICAL TREATMENTS

Surgery aims to remove endometriosis lesions and restore normally anatomy. When endometriosis is found or suspected at the time of surgery, clinicians are recommended to surgically treat the disease in a “see and treat” approach as this is effective for reducing pain (221). Both laparotomy and laparoscopy are effective however, laparoscopy is associated with reduced recovery time and hospital stay (222). The excision or ablation of endometriosis are effective for stages I&II disease while excision is preferential for treatment of pain associated with advanced diseased (223,224). Excision also allows the surgeon and patient a possibility to retrieve a sample for histological analysis and confirmation (223,224).

SURGERY FOR PAIN WITH ENDOMETRIOSIS

The treatment of pain associated with endometriosis surrounds three general techniques; removal or destruction of endometriotic lesions, interruption of nerve pathways, and division of adhesions. All of these techniques have moved from open laparotomy to minimally invasive laparoscopic or robotic procedures. The efficacy of laparoscopy compared to laparotomy has not been proven but the morbidity and recovery time following surgery is significantly less with laparoscopy (222).

Techniques to interrupt the nerve pathways supplying the pelvic organs have evaluated Laparoscopic Uterosacral Nerve Ablation (LUNA) and Pre-sacral neurectomy (PSN). These interrupt the uterosacral nerves severing the nerve pathways from the central nervous system along the uterosacral nerve leading to the uterus (LUNA) or pre-sacral nerve plexus overlying the sacral promontory. LUNA has been demonstrated to add no additional benefit at 1 year following surgery while the additional use of PSN is beneficial at 6 months and 1 year postoperatively. There are increased complications associated with PSN compared to LUNA including; bleeding, constipation, urgency of urination, and painless first stage of labour (225).

SEVERE ENDOMETRIOSIS

Deep infiltrating endometriosis (DIE) is the presence of endometriosis at 5mm or greater depth from the peritoneal surface and can involve the uterosacral ligaments, vagina, bowel, bladder or ureters (226). Pain is the cardinal symptom of DIE (227) with studies suggesting increasing intensity with severity of disease (228). Surgical treatments of DIE reduce pain and improves QOL (77,229,230) but this was not found to be more efficacious when compared to medical treatment (231). Different surgical techniques have been identified including shaving of endometriotic nodule, disc excision, and segmental bowel resection with end-to-end anastomosis or stoma formation. All treatments appear to significantly improve outcomes of pain with higher complication rates associated with bowel resection (232,233). The fertility outcomes following surgery for deep infiltrating endometriosis are less clear with no robust evidence to suggest significant benefit (234). Hysterectomy with bilateral salpingoophorectomy is advised when women have completed their families and failed other forms of more conservative treatment (235). The long-term outcomes of premature iatrogenic ovarian failure are poorly understood and therefore covered in chapter 8.

SURGERY FOR OVARIAN ENDOMETRIOSIS ASSOCIATED WITH PAIN AND INFERTILITY.

There are many different surgical techniques for the management of ovarian endometrioma including, cystectomy, fenestration, drainage, fenestration and ablation. Cystectomy is historically the surgical technique of choice. This involves opening the ovarian cortex, identifying the cyst wall and stripping this from the healthy ovarian tissue. In the presence of endometrioma, surgical treatment has been advocated as the treatment choice of pelvic pain, dyspareunia, improved sexual function, and enhanced spontaneous conception (236,237).

The benefits associated with IVF outcomes are less clear. A Cochrane review assessed multiple spontaneous and assisted fertility outcomes following cystectomy vs fenestration

and electro-cautery. The results favoured cystectomy with increased spontaneous conception rates, reduced recurrence, and increased ovarian response to gonadotrophin use during assisted reproductive technology (ART) (238). Subsequent meta-analyses have shown no significant improvement in pregnancy outcomes associated with surgery vs no surgery for ovarian endometrioma prior to ART (239–242). Please see chapter 7 for further discussion on the surgical management of endometrioma amongst patients with subfertility.

SURGERY FOR INFERTILITY WITH ENDOMETRIOSIS

There is a relationship between endometriosis and infertility as discussed previously (1.4.2) (243,244). Surgery for peritoneal disease has been assessed with two randomised controlled trials where combined meta-analysis demonstrated a benefit for spontaneous conception (221,245). There is no known pathway to explain this process (245).

MENOPAUSE IN WOMEN WITH ENDOMETRIOSIS

Oestrogen with or without progestagens are common hormonal treatments for women with menopausal symptoms arising from a physiological change to a hypoestrogenic environment. Endometriosis is an oestrogen dependent disease raising concern that post menopausal administration of exogenous oestrogen may result in recurrence or reactivation of endometriosis. Recurrence of endometriosis symptoms and active lesions has been observed in those having had a hysterectomy, bilateral oophorectomy and HT (211). The use of tibolone is recommended for the treatment of menopausal symptoms for those women who undergo the surgical menopause until they reach the mean age of menopause (211).

Endometriosis is currently managed with both surgical and medical modalities often in combination. Where combined medical and surgical strategies meet, accurate measurement and reporting of outcomes relevant to both treatments, clinicians, researchers, and patients is critical. Endometriosis remains a poorly understood disease and the lack of aetiological clarity can lead to multidirectional research that prevents comparability and threatens the advancement of patient care. Across all diseases there is a desire to generate patient centred clinically meaningful outcomes while basic science researchers further the understanding of this enigmatic disease.

Randomised controlled trials and systematic reviews evaluate interventions by comparing outcomes chosen to reflect beneficial and harmful effects. A systematic review cannot perform meta-analysis if the outcomes reported are diverse and heterogeneous. A scoping exercise of RCTs published in endometriosis between January 2013- October 2014 revealed 6 published trials reporting 37 separate outcomes, averaging 6 outcomes reported per article. Three studies reported dysmenorrhea, dyspareunia (246–248), two trials reported post-operative pain (246,249) two trials reported pregnancy and ectopic pregnancy (247,250) two trials reported irregular vaginal bleeding (246,250). The remaining 31 outcomes were assessed by individual trials. This limited search and scoping exercise suggests that only 16% of all outcomes reported in Endometriosis RCTs are comparable while those commonly reported outcomes of dysmenorrhea, dyspareunia and pregnancy are reported by only 50% or less of all trials. Such heterogeneity, if reflective of all trials, results in substantial outcome reporting bias and an inability to synthesise results across studies in systematic reviews. Outcome reporting bias is the selection for publication of a subset of the original recorded outcome variables on the basis of the results and/or incomplete reporting of outcome data. A recent study examined the prevalence of outcome reporting bias and its impact on Cochrane reviews (251). When adjusting for outcome reporting bias the treatment effect

estimate became non-significant in 19% of reviews and 26% would have overestimated the treatment effect by 20% or more.

This diversity in peer-reviewed publications can have a knock-on effect with guideline generation and interpretation of research for public dissemination. This is a small number of trials from a limited period of time, and provided the basis for chapters 3,4, & 5.

1.8 AREAS OF UNCERTAINTY

There remains great uncertainty within the diagnosis and management of endometriosis. The generalisability and non-specific nature of many of the symptoms together with the lack of a non-invasive diagnostic test can account for delays in disease diagnosis, treatment and symptom control. The variation in published research prohibits comparison, restricting the development of guidelines and use of structured treatment pathways. This allows for discrepancies and variation in the provision of practice, formal guidance and patient information internationally.

1.9 AIMS OF THE THESIS

Section 1. Diagnostic evaluation

1. To review the current non-invasive diagnostic strategies for endometriosis (Chapter 1)
2. To assess the diagnostic accuracy of CA-125 for the detection of histologically confirmed endometriosis (chapter 2)
3. To assess the diagnostic accuracy of CA-125 for the detection of endometriosis in a cohort of women with pain or subfertility (Chapter 3)

Section 2. Methodology evaluation

4. To assess the quality of published trials for researchers working in the field of endometriosis (Chapter 4)
5. To assess the quality of online information available to patients suffering with symptoms suggestive of Endometriosis (Chapter 5)
6. To assess the quality of national and international endometriosis guidelines for clinicians working with patients suffering from endometriosis. (Chapter 6)

Section 3. Therapeutic evaluation

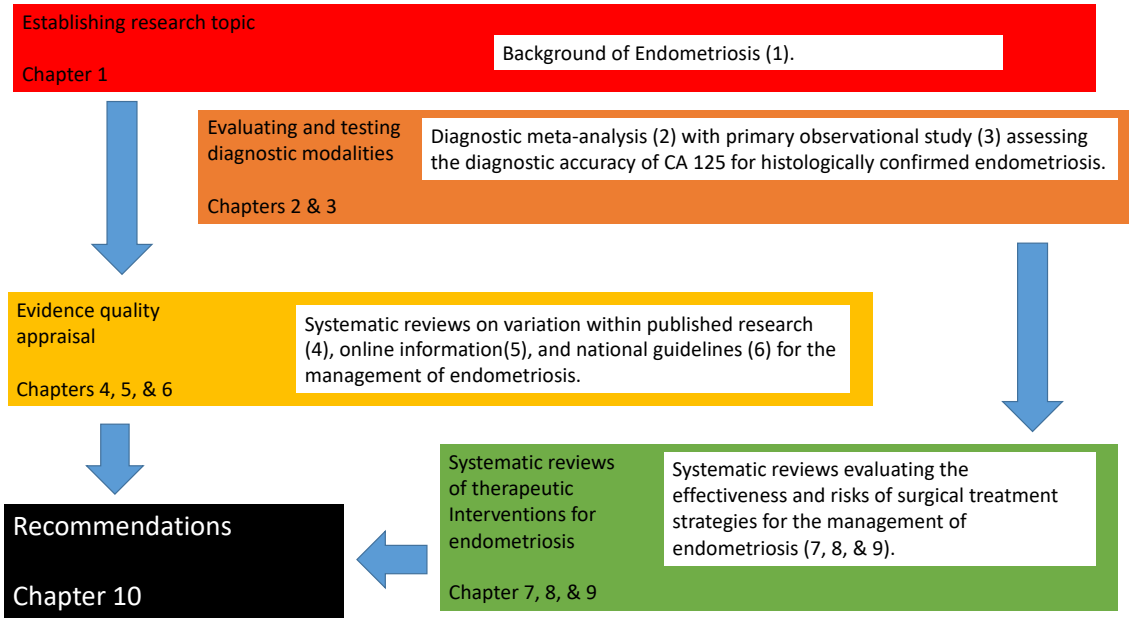
7. To review the risks of surgery for women with endometrioma (Chapter 7)
8. To assess the risks of female surgical castration for the management of endometriosis. (Chapter 8)
9. To assess the role of music in the recovery from endometriosis surgery (Chapter 9)

Table 1 - *Framing the research question*

Chapter Number	Population	Intervention/test	Outcome	Study design
2	Women with endometriosis symptoms	Serum CA-125	Histological endometriosis	Systematic review and Diagnostic meta-analysis
3	Women with pain and/or subfertility	Serum CA-125	Histological endometriosis	Prospective observation study
4	Patients with endometriosis	Outcomes and outcome measures for endometriosis	Quality of outcome reporting	Systematic review
5	Websites with information on endometriosis	Quality Readability Accuracy Credibility	Quality assessment of online information	Systematic review
6	National Guidelines on the management of endometriosis	AGREE II assessment tool	Quality and variation within national guidelines	Systematic review
7	Patients with ovarian endometriosis and subfertility	Surgical treatment options	Fertility	Literature review
8	Patients undergoing hysterectomy and bilateral	Surgical techniques	Chronic health outcomes	Systematic review and meta-analysis

	oophorectomy			
9	Patients undergoing endometriosis surgery	Music	Pain, Anxiety, Satisfaction, analgesia requirements.	Systematic review and meta-analysis

Figure 6 – *Outlining the research question*



CHAPTER 2:

THE DIAGNOSTIC ACCURACY OF THE CA-125 FOR ENDOMETRIOSIS IN SYMPTOMATIC WOMEN – A SYSTEMATIC REVIEW AND META-ANALYSIS

This chapter focuses on assessing the diagnostic accuracy of the most commonly used serum test for the histological presence of endometriosis. There is significant verification bias associated with the visual diagnosis of endometriosis as discussed in chapter 1. The evaluation of non-invasive diagnostic biomarkers has not identified an accurate test for the detection of endometriosis.

3.1 ABSTRACT

Objective: To assess the diagnostic accuracy of serum CA-125 (CA-125) for the presence of histologically confirmed pelvic endometriosis in reproductive aged women.

Data Sources: The following databases were searched from inception to February 2015: 1) EMBASE (1980-2015), 2) Medline (1954-2015), and 3) Web of Science (1900-2015). There were no language restrictions and bibliographies were manually searched by hand.

Study Selection: Observational studies evaluating the accuracy of serum CA-125 (index test) for the diagnosis of histologically confirmed endometriosis (reference standard) were included. Exclusion criteria were studies comparing the accuracy of CA-125 for the detection of malignancy. Study selection, data extraction, and quality assessment was performed by two authors independently. The assessment of methodological quality was undertaken using Quality Assessment of Comparative Diagnostic Accuracy Studies (QUADAS-2) checklist. A bivariate hierarchical model was used to pool accuracy of data.

Result(s): Nineteen observational studies (15 cohort, four case-control), 3163 participants, met the inclusion criteria. 13 of 19 studies (2611 participants) included data eligible for meta-analysis and were entered into a bivariate hierarchical model. This produce pooled accuracy data of CA-125 ≥30 unit / milliliter for the detection of histological endometriosis. The pooled specificity was 91% (95% CI 89% - 94%) and sensitivity 51% (95% CI 35% - 66%). Positive likelihood ratio was 5.9 (95% CI 3.7 - 9.5); negative likelihood ratio was 0.5 (95% CI 0.4 - 0.7). The post-test probability of CA125 ≥30 unit / milliliter rises to 86%-95% in women experiencing pain or subfertility symptoms

associated with endometriosis. CA-125 was significantly more sensitive for the diagnosis of moderate and severe endometriosis, using all cut-off values, compared to minimal and mild disease (62.6% 95% CI 44.6 - 77.6 vs. 24.8% 95%CI 18.8 - 32.1, p value=0.003). **Conclusions:** CA-125 continues to play an important role as a diagnostic serum biomarker in women with symptoms suggestive of endometriosis. Due to the poor sensitivity, we recommend limiting the use of this, rule-in, test to women with symptoms suggestive of endometriosis. The use of CA-125 ≥ 30 unit / milliliter has a high specificity for the detection of endometriosis when used amongst a symptomatic population.

Key words: endometriosis, non-invasive diagnosis, CA-125, biomarkers

3.2 BACKGROUND:

Endometriosis is a chronic oestrogen dependent disease defined by the presence of endometrial glands and stroma located outside the uterus. The disease is characterised by symptoms of pain and subfertility. Estimates of disease prevalence vary but are thought to be as high as 10% in the general female population and up to 75% of symptomatic women, yet it is commonly under-diagnosed (96). The current gold standard for diagnosis is laparoscopic visualisation, biopsy and histological confirmation. The invasive and time-consuming nature of referral for and performance of surgery accounts for a delay of 6-9 years from symptom onset to formal diagnosis (95–97). This time allows for disease progression, symptom deterioration and an annual societal cost of $49.6 Billion in the USA (101). The identification of an accurate non-invasive test for the detection of endometriosis is still ongoing (112,252). Women presenting to their General practitioner or gynaecologist with symptoms cannot receive a non-invasive test to include or exclude endometriosis. The discovery of a test which can rule-in endometriosis will reduce time to diagnosis, reduce disease progression, provide psychological reassurance, and offer additional treatment options (253). CA-125 (CA-125) is a well-established marker for epithelial cell ovarian cancer. This glycoprotein is derived from coelomic epithelia including the endometrium, fallopian tube, ovary, and peritoneum (117). CA-125 can be raised in endometriosis through direct stimulation of coelomic epithelia though its accuracy as a biomarker has been doubted (254). Studies evaluating the diagnostic accuracy of CA--125 for endometriosis have methodological limitations in patient selection (119,255–268), conduct of the index test (118,119,121,255,260–264,269–276), and verification of diagnosing the reference test (125,256–259,277–301). Two diagnostic reviews exists, however, one is over fifteen years old with a high risk of verification bias (116) and the second is low methodological quality (302).

In this chapter I aimed to perform a meta-analysis to assess the diagnostic accuracy of CA-125 for endometriosis.

A protocol with explicitly defined objectives, criteria for study selection, approaches to assessing study quality, and statistical methods was developed and prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42015017630, available online www.crd.york.ac.uk/prospero. We have reported the systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (303).

Search Strategy:

We performed a comprehensive and systematic literature review searching: 1) EMBASE, 2) MEDLINE, and 3) Web of Science for relevant citations from the date of inception to February 2015.

We used MeSH and free text combinations with Boolean logic of the following search terms: endometrio*, test*, diagnos*, accura*, marker, screen*, detect*, CA-125, CA-125, CA-125, CA125. There were no language or date restrictions. We searched the bibliographies of relevant articles by hand.

Study Selection

We included prospective and retrospective observational studies (cohort and case-control) assessing the diagnostic accuracy of pre-operative serum CA-125 to detect endometriosis confirmed by histology collected at robotic, laparoscopic, or open surgery. Exclusion criteria were malignancy. The patients were women undergoing surgery for the diagnosis or treatment of benign gynaecological diseases.

Data extraction and quality assessment

Titles and abstracts were screened independently by two reviewers (MH and JD). Full text of selective studies were critically reviewed the to assess eligibility. Any

discrepancies between the reviewers were resolved by discussion with a third author (KK).

Two reviewers (MH and JD) used a pilot-tested data extraction sheet to independently extract the data. The characteristics collected from each study included study design, setting, and participants. Where possible we extracted all relevant raw data from each study. Independent assessment of each study's methodological quality was performed in duplicate using the QUADAS-2 checklist. This checklist assessed: patient selection, conduct of the index test, conduct of the reference test, and patient flow. Studies were considered to be of high quality if they used consecutive recruitment to sample an appropriate patient spectrum using the index test before the reference standard, and all participants underwent the same reference standard (>85% histological analysis) (304). The following were considered study qualities with potential to introduce bias; patients with a pre-operative ultrasound diagnosis of endometriosis, case-control studies, and control groups that did not undergo the reference standard. These were assessed with subgroup and sensitivity analysis.

Outcomes:

We independently extracted data for the number of true positives, true negatives, false positives, and false negatives for the index test at the documented threshold in each individual study. Where raw data was unavailable in the text, the authors used the published sensitivities and specificities to calculate these data necessary to complete a 2 x 2 table. We actively contacted authors by email to seek clarification and requested missing data or additional data to complete our analysis (118,255,305,306). All discrepancies between the reviewers (MH and JD) were resolved through discussion with a third author (KK) or by contacting the authors.

Data synthesis:

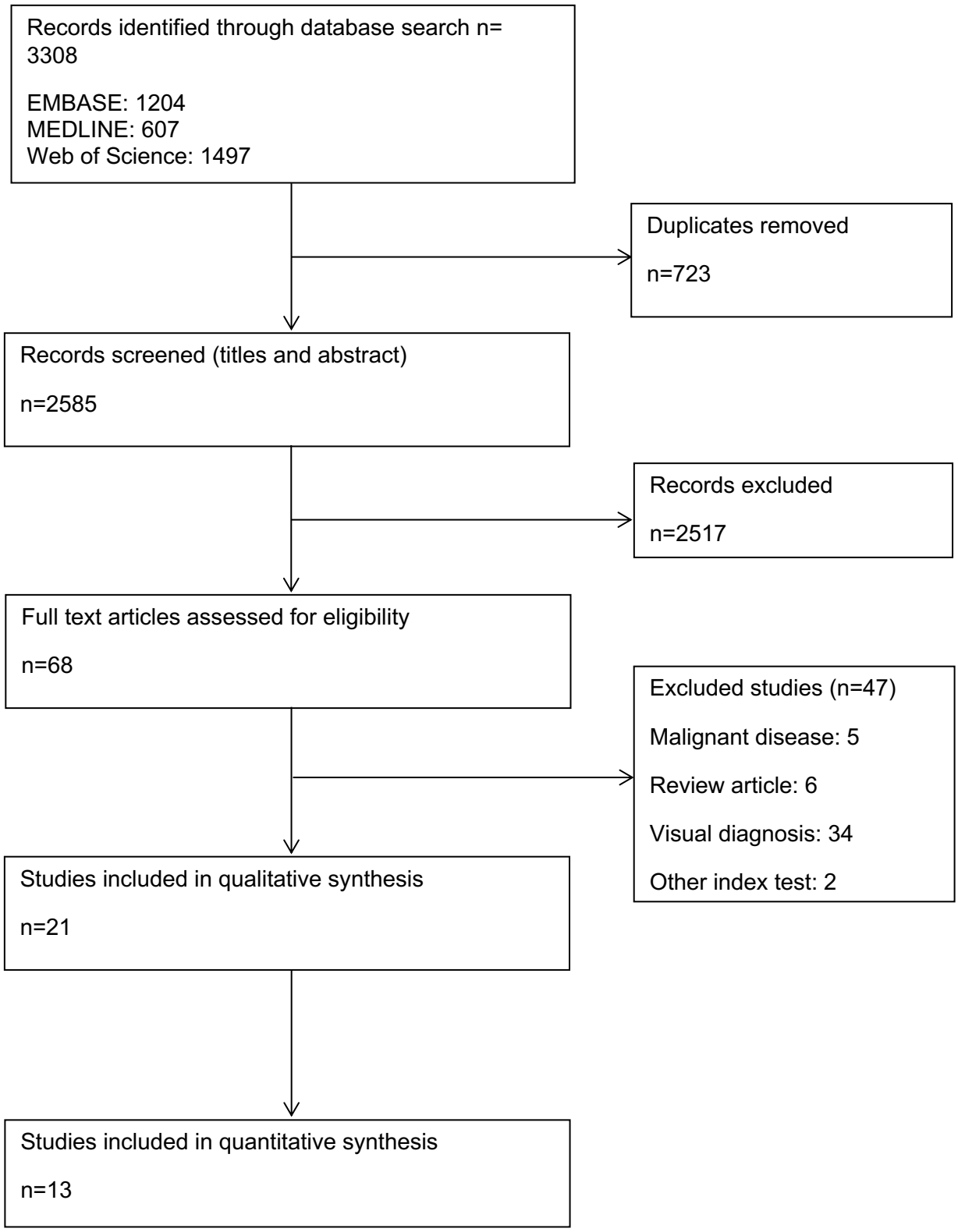
We constructed 2 x 2 tables for the detection of endometriosis for individual studies included in the review. Where studies reported multiple cut off values for CA-125 we

selected the closest value to the laboratory upper limit of normality (35 unit / milliliter) for our analysis (307). We explored variation in accuracy indices graphically using forests plots of sensitivity and specificity and receiver operative characteristics (ROC) plane plots of sensitivity against 1- specificity. As the studies used different cut-offs we grouped them in order to isolate subsets of studies using the same cut-off. In the case of no evidence of threshold effect within these subsets of studies, we fitted hierarchical bivariate random effects model (308) and obtained the following summary accuracy measures with corresponding 95% confidence intervals (CI): sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio. Post-test probabilities were calculated based on pooled estimates of likelihood ratios and overall pre-test odds based on published prevalence studies of endometriosis by clinical symptoms or signs. In case of evidence of threshold effects we summarised the analyses with the summary receiver operating characteristics curve. To investigate sources of heterogeneity, we performed subgroup analysis on the following: 1) comparison of study design (cohort vs. case-control), 2) comparison of positive ultrasound findings for endometriosis and negative or no ultrasound prior to test, 3) comparison of revised American Fertility Score (62,63) disease stage 1-2 versus 3-4. Sensitivity analyses were performed to evaluate the impact on accuracy of excluding studies that had elements of verification bias including 87% histological confirmation of endometriosis (119) and controls that did not undergo the reference standard (262). We checked differences in sensitivity and specificity between subgroups by adding covariates to the bivariate model. Stata software was used for statistical analyses. (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3.4 RESULTS:

Twenty-one studies recruited 3317 participants (7) (118–121,255,260–265,269–276,305,309,310). Two retrospective observational studies (119,262), and nineteen prospective observational studies (118,120,121,255,261,263–265,269–276,305,309,310) were included for analysis. Two studies did not include data that was analysable. The authors were contacted but did not respond, these studies were not included in the final analysis (255,305). A summary of the included studies is shown in figure 7.

Figure 7 - *Flow of included studies*



With the exception of Kitawaki 2005 (261), Cho 2008 (262), and Santulli 2015 (118) (Table 2), the studies were relatively small (n<300 participants). In accordance with World Health Organisation classification, all studies were conducted in high-resource settings (311). Recruitment occurred in a variety of settings including infertility clinics, fifteen studies (118–121,255,263–265,269,271,272,274,276,305,309) and general gynaecology clinic or elective gynaecological theatre sessions, seven studies (118,261,263,264,269,271,274). Twelve studies reported including patients with pain symptoms (118,120,121,261,264,265,269,271,274–276,305). Twelve studies recruited patients with pre-operative imaging available indicating an ovarian cyst (118,120,261–265,269–271,273,305). Endometriosis was confirmed by histology collected at either laparoscopic (63,118–121,263,265,269,272–276,305), laparoscopy or open (63,255,261,264,271) or did not specify the route of surgery (262,270). The staging of endometriosis was classified using the revised American Fertility Society classification 1985 (62) or the revised American Fertility Society classification 1997 (63). Nine studies (954 participants) included participants with minimal to mild endometriosis (255,262–265,271,272,305,309) and thirteen studies (1282 participants) included participants with moderate to severe endometriosis (121,255,262–265,271–273,275,305,309,310).

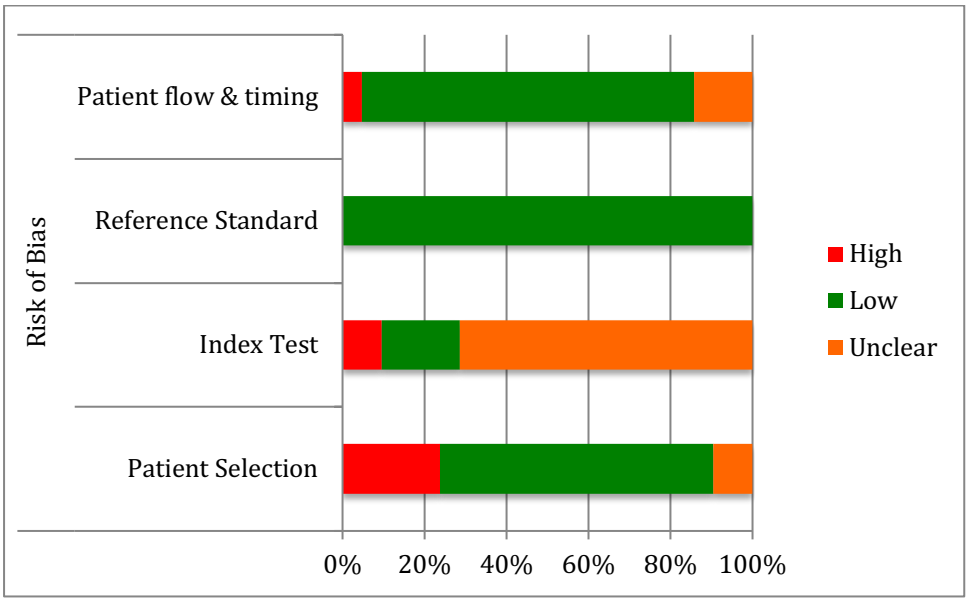
Table 2 - *Characteristics of included studies*

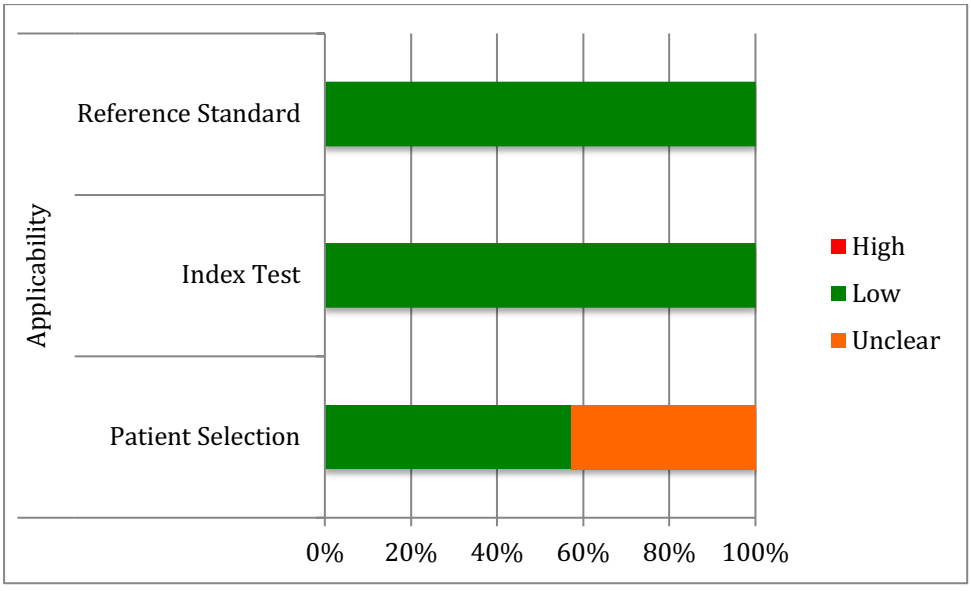
Author	Year	Country	Participants	Cut Off (iu/ml)	Study Design	Participant Characteristics	Ovarian Cysts	Endometriosis staging criteria
Wild	1991	USA	93	16	cohort	infertility	no	rAFS 1985
Adamyan	1993	USSR	49	35	case - control	cysts	yes	rAFS 1985
Molo	1994	USA	35	35	cohort	Infertility	no	rAFS 1985
Abrao	1997	Brazil	50	n/a	case - control	Not specified / tubal reanastomosis	yes	rAFS 1985
Chen	1998	Taiwan	99	35	cohort	pain	no	rAFS 1985
Kitawaki	2005	Japan	350	30	cohort	gynaecology referral / pain / cysts	yes	rAFS 1997
Amaral	2006	Brazil	52	25	cohort	infertility / pain / tubal ligation	no	rAFS 1997
Cho	2008	South Korea	760	35	case - control	elective gynaecological surgery / cysts	yes	rAFS 1997
Gajbhiye	2008	India	77	35	cohort	infertility department / cysts	yes	rAFS 1997
Jing	2008	Japan	61	16.3	case - control	pain / Infertility / cysts	yes	rAFS 1997
Salahpour	2009	Iran	60	14.7	cohort	pain / infertility / miscarriage	no	rAFS 1997
Kurdoglu	2009	Turkey	127	35	cohort	pain / infertility / general gynaecology / cysts	yes	rAFS 1997
Florio	2009	Italy	99	32	cohort	endometrioma vs other cysts	yes	rAFS 1997
Tokmak	2011	Turkey	88	21.3	cohort	cysts	yes	rAFS 1997
Vodolazkaia	2012	Belgium	296	12.5	cohort	infertility / biobank	no	rAFS 1997

Ramos	2012	Brazil	104	n/a	cohort	pain / infertility / tubal ligation / cysts	yes	rAFS 1997
Mohammed	2013	Egypt	60	35	cohort	pain / Infertility	no	rAFS 1997
Sayan	2013	Turkey	100	29.9	cohort	pain / infertility / general gynaecology / tubal ligation / cysts	yes	rAFS 1997
Kubatova	2013	Turkey	73	35	cohort	Pain / infertility / cysts	yes	rAFS 1997
Bilibio	2014	Brazil	97	35	case - control	pain / infertility / tubal ligation	no	rAFS 1997
Santulli	2015	France	685	35	cohort	pain / infertility / tubal surgery / cysts	yes	rAFS 1997

Risk of bias was assessed by two authors using the revised assessment tool: QUADAS2 and is represented in figure 8.

Figure 8 - *Quality Assessment using QUADAS2 Assessment tool*



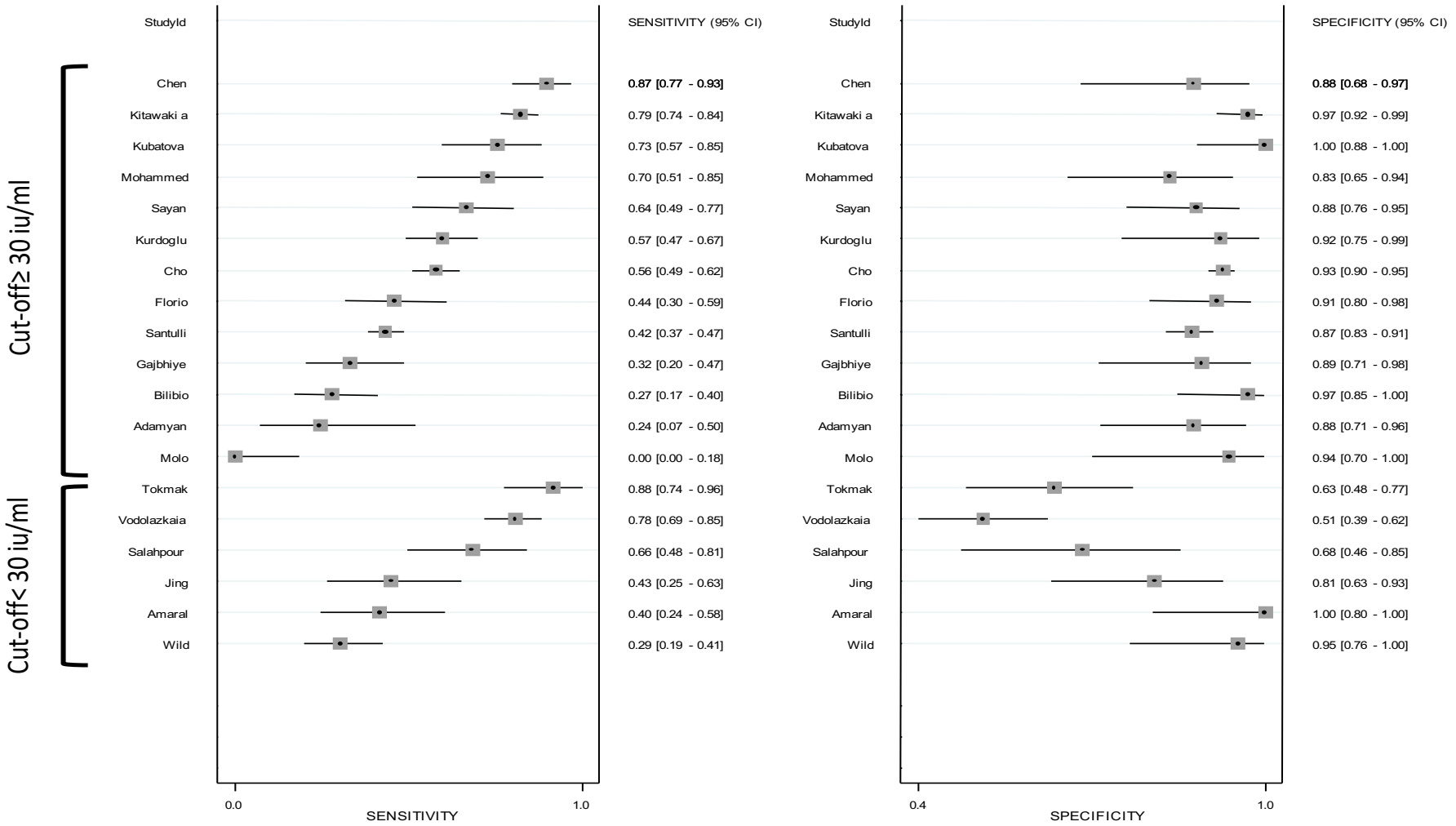


Seventeen of the 21 studies had a low risk of bias owing to patient timing and flow. One study (262) was described as high risk of bias as the asymptomatic control group did not

undergo surgery. A low risk of bias attributed to the reference standard for all studies as this was deemed an objective histological assessment. One study analysed the index test after the reference standard (119), while a further study performed the index test following the reference standard (255) and were deemed high risk of bias. A diagnostic cut off level for CA-125 was not specified a priori in 15/21 studies, these were classified as an unclear risk of bias (118,121,261–264,269–276,297). Fourteen studies had a low risk of bias owing to patient selection; five were high risk owing to case-control design (119,261–265) and the remaining two were unclear (119,264). Blinding of the surgeon to the index test prior to the conduct of the reference standard was reported in eight studies (119,255,263,265,269,276,305,309), thirteen studies were unclear in their description. CA-125 is an objective laboratory test result however, bias could be introduced to the conduct of the reference standard if the surgeon is aware of the CA-125 result. All studies were low risk for the index and reference standard with regard to applicability concerns. Twelve studies were low risk for patient selection and nine studies unclear owing to case-control design and inclusion of patients for tubal surgery, as this group may not routinely be screened for endometriosis (118,255,261–263,265,271,274,305).

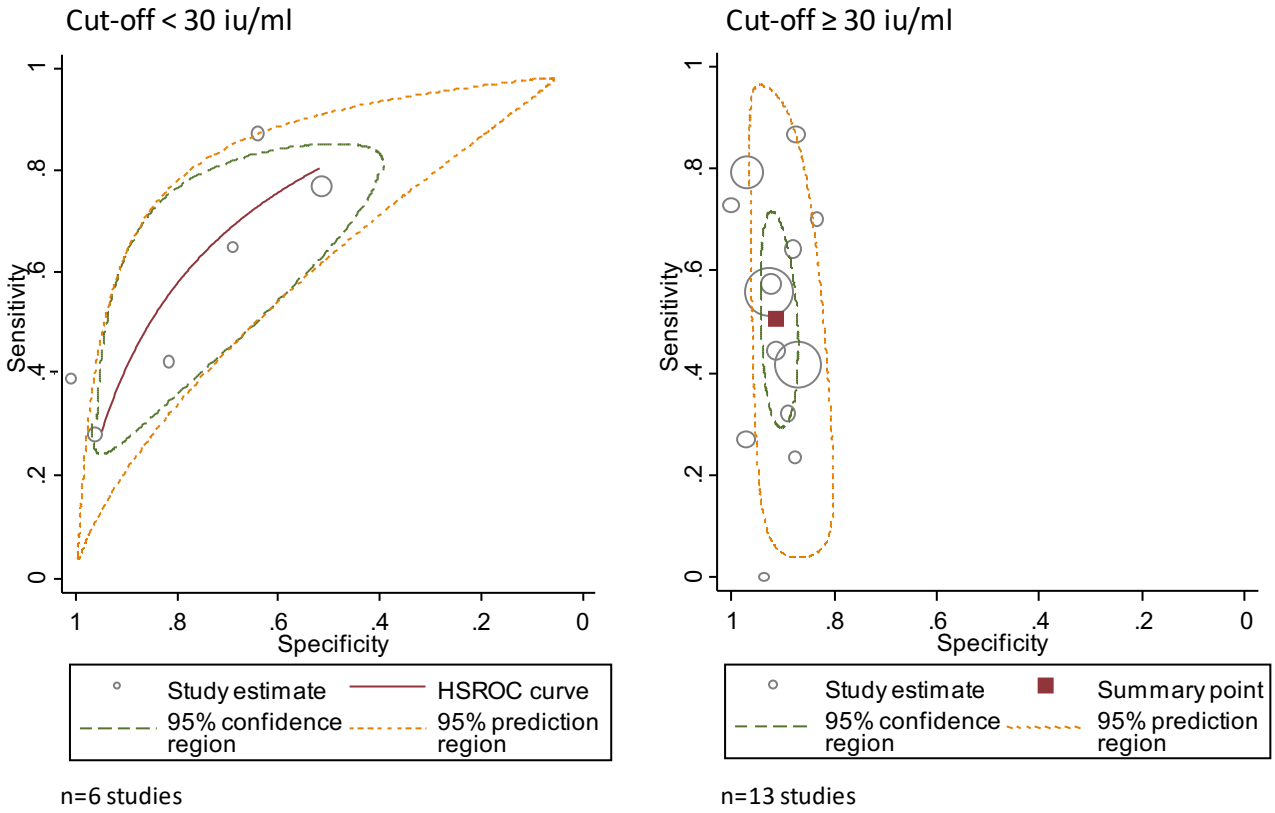
The variation in sensitivity and specificity between individual studies for the detection of pelvic endometriosis with serum CA-125 measurement is illustrated well in forest plots (figure 9). Individual study sensitivities ranged from 0% (272) to 87% (275) and specificity from 51% (119) and 100% (120).

Figure 9 - *Forest plots of sensitivity and specificity sorted in descending order of sensitivity, stratified by cut-off (CA-125 > 30 or <30 iu/ml).*



Thirteen studies, 2611 participants (1387 with endometriosis, 1224 controls) were meta-analysed to assess the accuracy of CA-125 ≥ 30 unit / milliliter for the presence of endometriosis (121,261–265,270–272,275,279,309,310). Pooled sensitivities and specificities for the 13 studies is summarised in figure 10 (right panel). Serum CA-125 ≥ 30 unit / milliliter had a pooled sensitivity of 50.6% (95% 35.3-65.8) and specificity 91.4% (95% 88.6-93.6). There was no apparent correlation between sensitivity and specificity. A sensitivity analysis which excluded an outlier study with 0% sensitivity (272) did not significantly alter results. This data is not shown. When we analysed a mix of cut-off points for CA-125, a high variation in both sensitivity and specificity was observed (Figure 10, left panel). There was a clear threshold effect which made the accuracy estimates of this subgroup less useful.

Figure 10 - *Summary Receiver Operating Characteristic Curves (CA-125 < 30 or ≥ 30 iu/ml)*



For the detection of endometriosis, the positive likelihood ratio was 5.9 (95% 3.7-9.5) and the negative likelihood ratio was 0.5 (95% 0.4-0.7). Fagan's Nomogram was used to calculate post-test probabilities and the likelihood of a positive test reflecting disease presence. This predictive tool is used to test the accuracy of a positive test amongst a disease with varied prevalence depending on clinical symptoms. For illustrative purposes Table 3 has split data into three groups, the general female reproductive population (10% pretest probability), women with subfertility (50% pretest probability) and those women with treatment resistant chronic pelvic pain (70-90% pretest probability) (91,96,312). Patients with a pretest probability of 75% and CA-125 ≥ 30 unit / milliliter will have a 95% likelihood of pelvic endometriosis.

Table 3 - *Pre and post-test probability of disease presence.*

Clinical Characteristics	Pre-test Probability	Positive Likelihood Ratio	Positive Post-test Probability*	Negative Likelihood Ratio	Negative Post-test Probability*
General population	10%	5.9	40%	0.5	5%
Subfertility	50%	5.9	86%	0.5	33%
Chronic Pelvic Pain	75%	5.9	95%	0.5	60%

* Derived from Fagan's Nomogram.

We highlighted sources of heterogeneity as study design (case-control versus cohort), the pre-operative ultrasound diagnosis of ovarian endometrioma and disease stage. Table 4 summarises these sources of heterogeneity. CA-125 showed higher sensitivity with increasing disease severity, 24.8% (95% 18.8-32.1 stage I-II) versus 62.6% (95% 44.6-77.6 stage III-IV). No significant differences were noted in pooled sensitivity and specificity for the detection of endometriosis in the presence or absence of ovarian cysts or change in study design. Sensitivity and specificity depend on the clinical situation in which the test is being applied. This varies between studies and results in clinical heterogeneity. Due to this clinical heterogeneity and the threshold effect, sensitivity and specificity are very heterogeneous in diagnostic meta-analyses. This limits the useful of testing for heterogeneity or using the *I*-square statistic to indicate the degree of heterogeneity (313).

Table 4 - *Sub-group analysis*

		Studies (n)	overall p value	Sensitivity (95% CI)	p value (relative sensitivity)	Specificity (95% CI)	p value (relative specificity)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)
CYSTS	with	11	p=0.928	56.4 (44 - 68)	p=0.538	90.0 (84.3 - 93.8)	p=0.991	5.6 (3.4 - 9.4)	0.5 (0.4 - 0.6)	11.6 (5.7 - 23.6)
	without	9		48.9 (28.9 - 69.2)		91.5 (79.0 - 96.9)		5.8 (2.7 - 12.3)	0.6 (0.4 - 0.8)	10.3 (4.5 - 23.6)
STUDY DESIGN	cohort	15	p=0.595	57.9 (43.2 - 71.3)	p=0.210	89.4 (81.7 - 94.1)	p=0.639	5.5 (3.2 - 9.3)	0.5 (0.3 - 0.6)	11.6 (5.9 - 23.0)
	case-control	4		38.2 (25.3 - 53.1)		90.9 (85.7 - 94.4)		4.2 (2.1 - 8.3)	0.7 (0.5 - 0.9)	6.2 (2.5 - 15.3)
DISEASE STAGE	stages III-IV	10	p=0.006	62.6 (44.6 - 77.6)	p=0.003	90.3 (83 - 94.7)	p=0.513	6.5 (4.0 - 10.4)	0.4 (0.3 - 0.6)	15.6 (8.4 - 29.0)
	stages I-II	6		24.8 (18.8 - 32.1)		92.2 (89.9 - 94.0)		3.2 (2.2 - 4.6)	0.8 (0.7 - 0.9)	3.9 (2.5 - 6.2)

Overall p-value refers to the likelihood ratio test of including in the model variation in both sensitivity and specificity.

We performed sensitivity analyses excluding studies with verification limitations (119,262) and this did not change accuracy estimates of CA-125 for detecting the presence of endometriosis (Table 5).

Table 5 - *Sensitivity analyses*

		Studies	**Diseased / Non diseased**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive Likelihood Ratio (95% CI)**	**Negative Likelihood Ratio (95% CI)**	**Diagnostic Odds Ratio (95% CI)**
Cutoff Level ≥ 30	Total	13	1387/ 1224	50.6 (35.3-65.8)	91.4 (88.6-93.6)	5.9 (3.7-9.5)	0.5 (0.4-0.7)	10.9 (5.0-23.7)
	Sensitivity analysis*	12	1156/ 695	49.9 (33.1-66.7)	91.3 (87.5-94)	5.7 (3.3-9.9)	0.5 (0.4-0.8)	10.4 (4.4-24.8)

**(Without Cho & Vodolazkaia studies)*

		Studies	**Diseased / Non diseased**	**Sensitivity (95% CI)**	**Specificity (95% CI)**	**Positive Likelihood Ratio (95% CI)**	**Negative Likeloihood Ratio (95% CI)**	**Diagnostic Odds Ratio (95% CI)**
Cutoff Level < 30	Total	6	331/ 221	58.1 (39.7-74.5)	79.4 (60.1-90.8)	2.8 (1.6-4.8)	0.5 (0.4-0.7)	5.3 (3.0-9.5)
	Sensitivity analysis*	5	214/ 140	54.6 (33.6-74.2)	83.2 (67.8-92.1)	3.3 (2.0-5.4)	0.5 (0.4-0.8)	6 (3.1-11.3)

**(Without Cho & Vodolazkaia studies)*

3.5 DISCUSSION:

This chapter has been able to demonstrate that the use of serum CA-125 ≥ 30 unit / milliliter is highly specific for the detection of histologically confirmed pelvic endometriosis amongst symptomatic women. The high levels of specificity achieved in symptomatic women provides the possibility of using CA-125 > 30 unit / milliliter as a rule-in test. This would minimise unnecessary instigation of hormonal or surgical treatments. The index test does have a poor sensitivity for the detection of endometriosis and only 51% of those suffering having a CA-125 ≥ 30 unit / milliliter. A CA-125 test result of < 30 units / milliliter is unable to rule out the disease, optimising its use amongst a high risk symptomatic population.

This chapter is a summary of the first prospectively registered review comparing the accuracy of CA-125 with the histological presence of endometriosis. We conducted a comprehensive search strategy, robust methodology, and statistical analysis. All studies included reported the primary endpoint using the reference standard of histologically confirmed endometriosis. While the sensitivity is poor, the high specificity indicates a low risk of false positive result. This minimises patient harm through unnecessary surgical procedures or hormonal treatments. This offers specialist and generalist clinicians confidence in a positive test providing a diagnosis and instigating management of this enigmatic disease. This has potential for providing a resource to diagnosis and medical management in countries without access to safe laparoscopic surgery. There are several other gynaecological diseases that cause a rise in CA-125 these include, ovarian epithelial carcinoma, leiomyoma, and pelvic inflammatory disease. A previous systematic review was published over 15 years ago with associated verification bias (116). Our meta-analysis addresses these methodological inadequacies.

Methodological inadequacies include the use of case-control studies (121,256–259,262,265–268,276). These studies have large discrepancies between the anticipated

prevalence of the groups. To analyse the effect of these sources of bias on heterogeneity, we performed sub-group analysis with case-control studies and found a non-significant change in sensitivity and specificity (Table 4). There was variation in CA-125 assay assessment which could introduce bias.

To counter the previously observed verification bias, our selection criteria excluded many high quality studies that did not use histological confirmation of endometriosis as the reference standard. This leads to selection and publication bias. Patient recruitment, index, and reference standard sampling occurred at various stages within the menstrual cycle but whether this influences CA-125 level is not well established (278,314). Homogenous secondary outcome sub-group meta-analysis was not possible as only three studies assessed infertility or pelvic pain separately.

There is currently no accurate non-invasive test for the detection of endometriosis. This meta-analysis demonstrates a role for the use of CA-125 in women presenting with pain or infertility. Diagnosis allows women relief, liberation and legitimisation of their symptoms including access to support and an opportunity to discuss medical or surgical management (253). CA-125 could play a role in both surgical and family care settings. In the surgical setting, CA-125 can aid physician-patient decision making in symptomatic women where laparoscopy would confer benefit. In family care practices, CA-125 should be offered to symptomatic women who would benefit from hormonal use or referral to a gynaecologist. For positive post-test probability by pretest risk see table 3. CA-125 has limitations with a poor sensitivity of 51%. This limits the use of CA125 to women with symptoms of endometriosis where there is high suspicion of disease. The indiscriminate use of CA-125 should be avoided in favour of a targeted rule-in test for symptomatic women and their clinicians wishing for further confidence in diagnosis prior to delivering a therapeutic intervention.

In the absence of a more accurate test, this readily accessible and specific test can, when positive, provide additional treatment options, reduce time to diagnosis, and anxiety amongst endometriosis sufferers. We recommended further research assessing cost, quality of life, pain and fertility outcomes following the use of CA-125 to triage treatment modality for women in a pelvic pain or fertility clinic.

3.6 CONCLUSIONS:

In symptomatic women, the use of CA-125 $\geq$ 30 unit / milliliter is highly specific for diagnosing endometriosis. CA-125 < 30 unit / milliliter does not exclude endometriosis and further investigation is required. CA-125 has an important role as a diagnostic biomarker in women with symptoms suggestive of endometriosis.

This Chapter was based on the following peer reviewed publication (315):

Diagnostic accuracy of cancer antigen 125 for endometriosis: a systematic review and meta-analysis.
Hirsch M, Duffy J, Davis CJ, Nieves Plana M, Khan KS; International Collaboration to Harmonise Outcomes and Measures for Endometriosis.
BJOG. 2016 Oct;123(11):1761-8.

CHAPTER 3:

THE DIAGNOSTIC ACCURACY OF CA-125 – A PRIMARY DIAGNOSTIC STUDY

This chapter addresses the recommendations from chapter 1. We conducted a prospective observational cohort study assessing the diagnostic accuracy of CA-125 for the presence or absence of histological endometriosis in women with pelvic pain and or subfertility. This study aims to assess the sensitivity, specificity, positive, and negative likelihood ratios of a CA-125 ≥ 30 iu/ml predicting histologically confirmed endometriosis. The analysis of this chapter was informed and performed following the development of a cut off value of CA-125 ≥ 30 iu/ml generated in chapter 2. This was developed following commencement of recruitment for this study. The standardised cut off CA-125 ≥ 30 iu/ml will promote homogeneity of published research and the future synthesis of meta-analyses.

4.1 ABSTRACT

Study Objective: Endometriosis is associated with pelvic pain and subfertility affecting 10% of reproductive age women. There is currently no widely used non-invasive diagnostic marker. We aimed to assess the diagnostic accuracy of serum CA-125 > 30 iu/ml for predicting histological endometriosis in women with pelvic pain or subfertility.

Design: Prospective observational cohort study. 58 women with pelvic pain or subfertility were prospectively evaluated with questionnaires and serum CA-125 immunoassay.

Setting: Tertiary referral university hospital

Patients: Patients were included if they were scheduled for laparoscopic investigation of pain and or subfertility in the absence of other imaging or history assessed gynaecological pathology. We evaluated the accuracy of CA-125 (index test) with histological endometriosis (reference standard).

Interventions: Laparoscopic investigation of the abdomen and pelvis.

Measurements and Main Results: We recruited 58 patients with pelvic pain and or subfertility undergoing laparoscopy investigation. Women with endometriosis had a mean higher CA-125 level than those without endometriosis (54.7 +/-71.6 vs 16.2 +/- 8.0 p=0.006). The sensitivity of CA-125 ≥ 30 U/ml was 0.57 and the specificity was 0.96. The positive likelihood ratio for the histological presence of endometriosis with a CA-125 ≥ 30 U/ml was 15.8 providing a post-test probability of 94% in women with pain and or subfertility.

Conclusions:

This study demonstrates that CA-125 > 30 iu/ml is highly predictive of endometriosis in women with symptoms of pain or sub-fertility and no evidence of concomitant gynaecological pathology.

4.2 INTRODUCTION

Endometriosis is defined as the presence of endometrial glands and stroma located outside the uterus. It is a disease characterised by pain and subfertility. Disease estimates suggest a prevalence of 10% of reproductive age women and up to 75% of symptomatic women yet it is commonly under-diagnosed (315). The gold standard diagnostic test is surgery, visualisation, biopsy and histological confirmation. Evaluation of non-invasive diagnostic biomarkers has not identified an accurate test for the detection of endometriosis (316,317). Women presenting to their primary care physician or gynaecologist are unable to receive a non-invasive test that can include or exclude endometriosis. A rule in test can reduce time to diagnosis, provide psychological reassurance, offer treatment options, and reduce disease progression (253). Cancer Antigen-125 (CA-125), a well-established marker for epithelial cell ovarian cancer, is derived from coelomic epithelia including the endometrium, fallopian tube, ovary, and peritoneum (318). CA-125 is raised in endometriosis through stimulation of coelomic epithelia (254). Previous diagnostic accuracy studies have suffered from verification bias (visual diagnosis) or design bias (all case control).

The aim of this present study is to assess the diagnostic accuracy of preoperative serum CA-125 levels in a cohort of women with pain or subfertility for the diagnosis of histologically confirmed endometriosis.

4.3 METHODS

Study Design

The local ethics committee approval was sought for the study protocol. This study was conducted as a prospective observational cohort study. The cohort included women with pelvic pain and or subfertility undergoing laparoscopic investigation.

Patient selection and data collection

All included patients signed a written informed consent form. The study commenced in October 2013 and we prospectively collected consecutive clinical data from women referred for investigation of pelvic pain and or subfertility under the care of the benign / reproductive gynaecological teams at The Royal London and St Bartholomew's Hospital. The definition used for pelvic pain was a visual analogue score (VAS) of > 50 on a VAS 0-100 for dysmenorrhea, dyspareunia or chronic pelvic pain. The definition used for subfertility was unexplained failed conception after 12 months of regular (>twice/week) unprotected vaginal intercourse (319). Patients were excluded if they were believed to have or previously had a condition other than endometriosis which can cause a raised CA-125. These conditions included previous or suspected; leiomyoma, adenomyosis, pelvic inflammatory disease, mature cystic teratoma, mucinous cystadenoma, and hydrosalpinges. They were evaluated with either ultrasound, MRI, or medical history. Women with a history of any malignancy or those who did not consent were excluded from analysis.

Participants were recruited consecutively and consented prior to surgery and serum samples were collected preoperatively for CA-125 immunoassay measurement. The participants underwent routine operative surgical management from surgeons working within a national endometriosis centre with over ten years' experience of diagnosing and managing endometriosis. The surgeons performing the procedures were blinded to the result of the CA-125 test that was processed in a NHS quality controlled laboratory within

4 hours of sampling. Laparoscopy was performed and all recognisable endometriosis lesions were biopsied and then treated by bipolar coagulation, resection of endometriosis nodules or ovarian cystectomy. In accordance with ESHRE guidance (107), histological confirmation of disease was attempted but not possible in all cases of suspected endometriosis. As the diagnosis of endometriosis stage 1 / 2 has poor accuracy based on visual diagnosis alone (64), the authors decided to exclude those patients without histological confirmation of disease. Those patients with visually confirmed endometriosis or other pelvic pathology at the time of surgery were excluded from the primary analysis.

Data was collected during face-to-face interviews with each patient by a single researcher (MH) in the preoperative assessment area. We collected demographic information for all patients including age, gravidity, parity, age at menarche, stage of menstrual cycle, smear history, previous surgery, medication, infertility duration, smoking status, alcohol status, and contraceptive use. Pain symptoms were assessed prospectively using a visual analogue scale (VAS) 0-100mm for dysmenorrhoea, deep dyspareunia, dysuria, dyschezia, chronic pelvic pain, and mid cycle pain. We did not confound for hormonal use or stage of menstrual cycle.

The primary outcome was the diagnostic accuracy of CA-125 $\geq$ 30 iu/ml to detect the presence of histologically confirmed endometriosis. Secondary outcomes included assessing the association between CA-125 level and pain.

Statistical analysis

Statistical data were collected in a computerised database and analysed by SPSS software 18.0.0 (SPSS Inc., Chicago, Illinois). We compared the clinical characteristics between those with endometriosis and those without, summarising the characteristics of the two groups using standard statistics. These two groups were classified as either reference standard (histological endometriosis) positive or negative. We then calculated

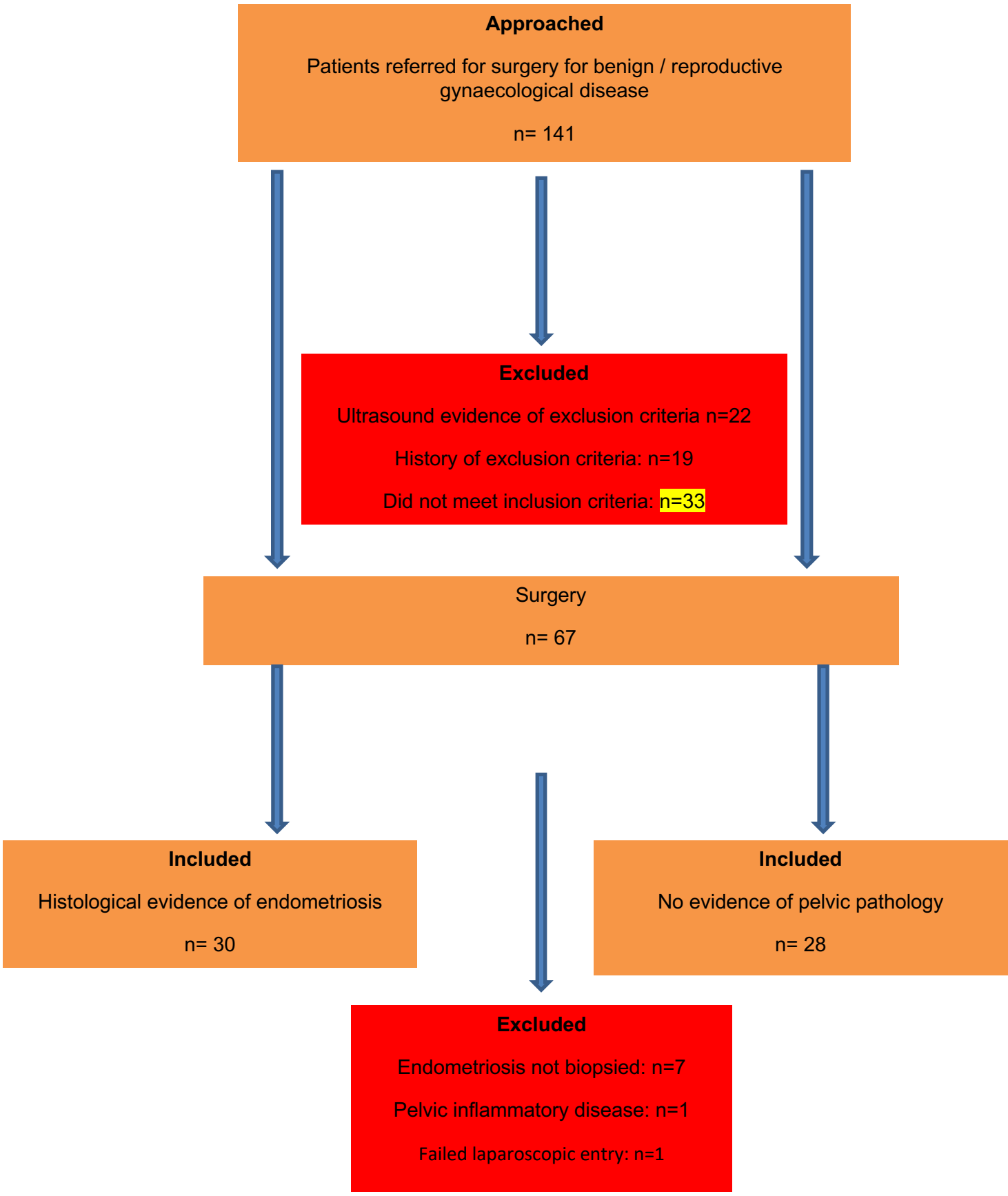
the area under the receiver operating curve (ROC), which quantifies the ability of the index test (CA 125) to distinguish between patients with and without endometriosis. Our sample size was chosen so that if the true AUC was 0.85, we would be able to estimate it to within 0.15 using a 95% CI [13]. This was performed retrospectively. Positive likelihood ratios and negative likelihood ratios were calculated and post-test probability was evaluated using these likelihood ratios and Fagan's Nomogram (320) based on a pre-test prevalence estimate of 50% in this group of symptomatic women (312).

4.4 RESULTS

Primary study

A total of 141 participants undergoing laparoscopic investigation of pelvic pain or subfertility were approached for recruitment. 102 met the previously described inclusion criteria. We prospectively recruited 67 women without evidence of PID, fibroids, ovarian cysts, (other than endometrioma), adenomyosis, or hydrosalpinges. Nine patients were excluded at the time of surgery: biopsy of suspected lesions was not possible (n=7); additional disease was noted (n=1); and failed laparoscopic entry (=1). One study participant who did not undergo the procedure due to failed laparoscopic entry secondary to insufflation of the pre-peritoneal space. This prohibited safe primary trocar insertion. The patient was observed overnight and followed up in clinic without complication. Fifty-eight women were included in the primary analysis (figure 11). Of those included, 28 had no macroscopic pathology and 30 were found to have histologically confirmed endometriosis (figure 11).

Figure 11 - *flow of included patients*



Clinical characteristics

Between October 2013 and October 2015, 141 patients were approached for entry into this study. We excluded 84 for the following reasons; suspected adenomyosis, suspected leiomyoma, previous pelvic inflammatory disease or sexually transmitted infection, previous malignancy, and visually suspected endometriosis. A total of 58 were included for analysis. The clinical characteristics of the patients are summarised in table 6. The patients were staged according the revised American Fertility Scoring for endometriosis and were classified as follows: 7 stage 1, 9 stage 2, 10 stage 3, 4 stage 4 (63). Twenty six patients were recruited during the follicular phase and 22 during the luteal phase of the menstrual cycle. We were unable to determine the phase of the menstrual in 10 patients due to hormonal contraceptive use.

Table 6 - *Participant Characteristics*

Baseline Characteristics	Endometriosis (n=30)	Controls (n=28)
Age, yrs	34.1	32.2
Primary Infertility, n (%)	14 (47%)	8 (29%)
Secondary Infertility, n (%)	3 (10%)	6 (21%)
Endometriosis Stage I-II, n (%)	16 (53%)	-
Endometriosis Stage III-IV, n (%)	14 (47%)	-
Mean CA-125 value u/ml	54.7 (SD 71.6)	16.2 (SD 7.97)
Hormonal contraceptive use, n (%)	5 (17%)	4 (14%)
Mean VAS (0-10cm) Dysmenorrhea	8.10 (SD 1.41)	6.49 (SD 2.97)
Mean VAS (0-10cm) Dyspareunia	5.26 (SD 3.31)	4.53 (SD 3.79)
Mean VAS (0-10cm) Dsychezia	3.77 (SD 3.41)	1.91 (SD 2.81)
Mean VAS (0-10cm) Chronic pelvic pain	3.81 (SD 3.80)	4.24 (SD 3.82)
Mean VAS (0-10cm) Dysuria	1.25 (SD 1.99)	0.73 (SD 1.72)

Primary results

The two groups were comparable for age. The mean age for those with confirmed endometriosis was 34.1 (SD +/- 5.9) and without endometriosis 32.2 (SD +/- 8.6).

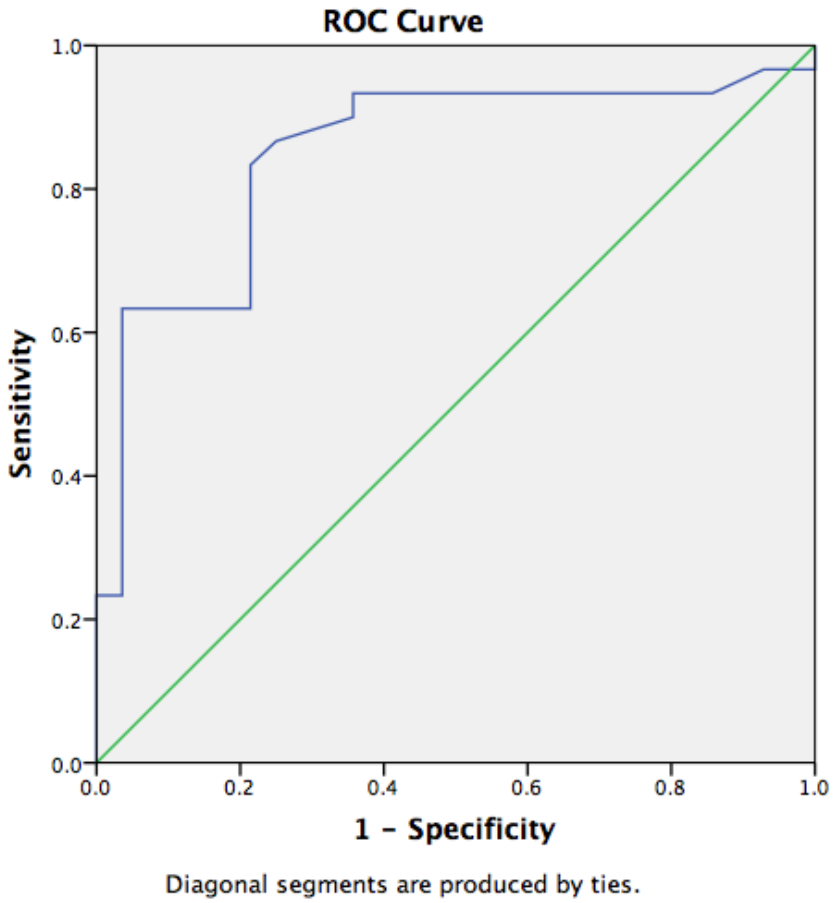
Mean CA-125 values

Thirty patients diagnosed with endometriosis had a mean CA-125 level was 54.7 (SD 71.6). Twenty eight participants with no macroscopic pathology had a mean CA-125 of 16.2 (SD 8.0). One patient had a CA-125 > 30 iu/ml without macroscopic gynaecological disease while 17 had both a CA-125 > 30 iu/ml and histological endometriosis. Thirteen patients had a CA-125 < 30 iu/ml in the presence of histological endometriosis while 27patients had a CA-125 < 30 iu/ml in the absence of macroscopic endometriosis.

Diagnostic accuracy

Receiver operating characteristic curve (figure 12) demonstrates the accuracy of CA-125 as a diagnostic test for endometriosis. The area under the curve, 0.85 (CI 0.74 – 0.96) indicates high test accuracy. The use of a predefined cut-off, CA-125 $\geq$ 30 iu/ml is based on a previously published meta-analysis (315). This will enable further data-synthesis in the future with a comparable cut off. The chosen cut-off value (30 iu/ml) demonstrated 57% (95% CI 37.4 – 74.5%) test sensitivity and 96% (95% CI 81.7 – 99.9%) specificity, and 76% diagnostic accuracy. The positive likelihood ratio of CA $\geq$ 30 iu/ml was 15.8 (2.3-112) producing a positive post-test probability of 94% amongst women with pain or subfertility in the absence of other gynaecological disease (table 7, figure 13). The negative likelihood ratio is 0.45 (95% CI 0.30-0.68) producing a negative post-test probability of 33% in women with CA < 30 u/ml and common gynaecological symptoms.

Figure 12 - *Receiver Operating Characteristics Curve*



Area Under the Curve

Test Result Variable(s): CA-125 iu/ml

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% CI	
			Lower Bound	Upper Bound
.850	.054	.000	.744	.956

The test result variable(s): CA125 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Table 7 - *Coordinates of the Curve Test Result Variable: CA-125 iu/ml*

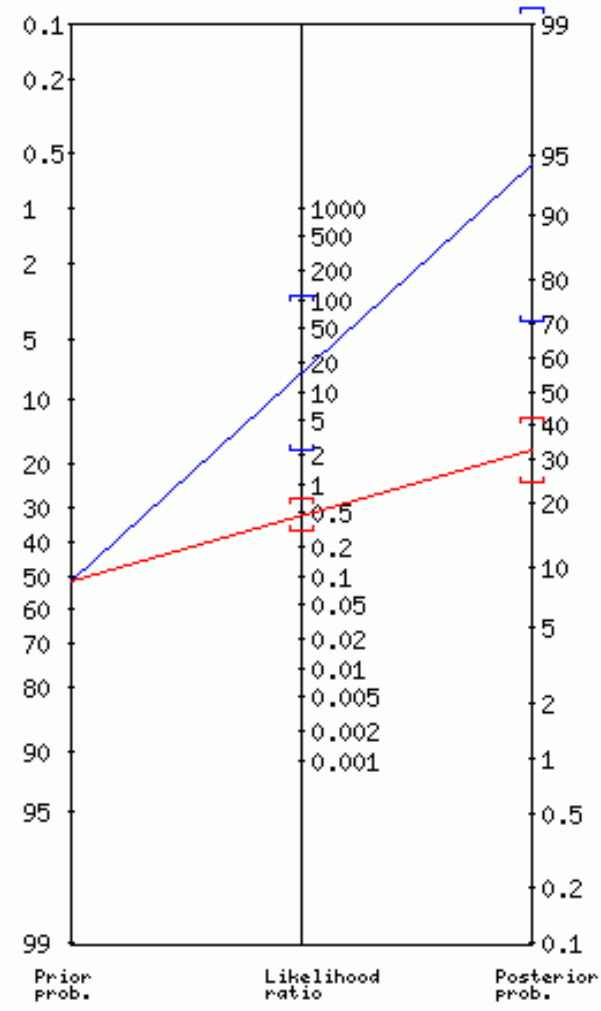
Positive if greater than or equal to	Sensitivity	Specificity
4.00	1.000	0
6.00	0.967	0
8.00	0.967	0.071
9.50	0.933	0.143
10.50	0.933	0.179
11.50	0.933	0.25
12.50	0.933	0.321
13.50	0.933	0.5
14.50	0.933	0.571
15.50	0.933	0.607
16.50	0.933	0.643
17.50	0.900	0.643
18.50	0.867	0.75
19.50	0.833	0.786
20.50	0.733	0.786
21.50	0.667	0.786
22.50	0.633	0.786
23.50	0.633	0.857
25.00	0.633	0.893
26.50	0.633	0.964
28.00	0.600	0.964
30.00	0.567	0.964
34.00	0.533	0.964
37.50	0.467	0.964
38.50	0.433	0.964
39.50	0.400	0.964
40.50	0.367	0.964
43.00	0.267	0.964
45.50	0.233	0.964
51.00	0.233	1
63.00	0.200	1
80.00	0.167	1
90.50	0.133	1
111.50	0.100	1
161.00	0.067	1
282.00	0.033	1
375.00	0.000	1

Secondary results

Pain symptoms

We compared pain symptoms between those with endometriosis and those without endometriosis. Individual patient values were combined to produce means with standard deviations (SD) calculated. The mean VAS for dysmenorrhea amongst those women with endometriosis was 8.10cm (SD 1.41cm), and for women without endometriosis was 6.49cm (SD 2.97cm). The mean VAS for dyspareunia amongst those women with endometriosis was 5.26cm (SD 3.31cm), and for women without endometriosis was 4.53cm (SD 3.79cm). The mean VAS for chronic, non-cyclical pelvic pain amongst those women with endometriosis was 3.81cm (SD 3.8cm), and for those women without endometriosis was 4.24cm (SD 3.82cm).

Figure 13 - *Fagan's Normogram*



POSITIVE TEST:

Positive Likelihood ratio:	15.75
95% CI:	[2.26,112]
Post-test probability (odds):	94% (17.1)
95% CI:	[71%,99%]

NEGATIVE TEST:

Negative Likelihood ratio:	0.45
95% CI:	[0.30,0.68]
Post-test probability (odds):	33% (0.5)
95% CI:	[24%,42%]

Main Findings

This primary cohort study indicates that CA-125 ≥ 30 iu/ml has a high accuracy for the detection of endometriosis in symptomatic women without evidence of other concurrent gynaecological disease. CA-125 provides limited sensitivity for the detection of endometriosis and a negative test cannot exclude endometriosis. In the absence of other accurate biomarkers, CA-125 > 30 iu/ml provides diagnostic confidence to both clinicians and patients.

Strengths

Strengths of this study include its robust design. We prospectively recruited a homogenous cohort of women with pain or subfertility. We blinded a select group of surgeons working at an endometriosis specialist centre to the outcome of the index test result. We reduced recruitment bias by limiting recruitment to be performed by a single individual and assay bias was minimised by the use of a single quality controlled NHS laboratory. We limited interpretation bias by using a pre-defined validated cut-off for the analysis. We minimised clinical heterogeneity by excluding participants with other diseases known to cause a raised CA-125.

Limitations

This study has limitations by its small sample size. We sampled the index and reference standard at varied times during the menstrual cycle, including those women on hormonal modulators. Although there is no clear influence of menstrual timing (314) nor hormones (321) altering CA-125 levels this introduces clinical heterogeneity. CA-125 is known to be raised in other benign and malignant gynaecological pathology. We attempted to confound for this by excluding all those patients with prior ultrasonographic or MRI

evidence of leiomyoma, adenomyosis, and hydrosalpinges, benign non-endometriotic cysts. We excluded those patients with a previous history of pelvic inflammatory or sexually transmitted disease. This study is limited by the small number included participants. There are ongoing limitations associated with the reference standard (visualisation, biopsy, and histological confirmation) used in this and many other studies. The presence of occult microscopic endometriosis endometriosis lesions has been confirmed on visually normal peritoneum, this introduces verification bias to this and all diagnostic accuracy studies(322).

Comparison with existing literature

Previous primary studies and systematic reviews have demonstrated a limited role for the use of CA-125 in the detection of endometriosis. These studies suffered from significant verification bias (visual detection), design bias (case-control studies) and cohort heterogeneity (varied recruitment strategies) (315). The sensitivity of CA-125 has repeatedly been demonstrated as poor with increasing accuracy associated with advancing stage of disease (315). The search for an accurate non-invasive biomarker for endometriosis remains elusive (252,323) despite it being highlighted a research priority in 2009 (106).

Interpretation

As confirmed by Mol et al 1998, CA-125 is an important biomarker with a role as a rule-in test for women with pain or subfertility (116). The sensitivity of this test remains poor, limiting its use to cohorts of symptomatic women with a high pre-test prevalence. The diagnosis of women with pain or subfertility and a normal ultrasound remains difficult. This study has attempted to address these difficulties.

This study demonstrates that when CA-125 $\geq$ 30 iu/ml is used amongst a defined population with a narrow inclusion criteria for testing, a positive result provides a very high post-test probability. The high specificity minimises false positive results and

unnecessary treatment exposure from hormonal therapies or surgical procedures. The implementation of CA 125 in primary care or hospital settings as a point of care test for women with pain or subfertility and a normal USS may decrease delays in the diagnostic pathway, allowing women relief, liberation and legitimisation of their symptoms, together with access to support and an opportunity to discuss individualised medical or surgical management.

Further research is required amongst a population of women with pelvic pain or subfertility and a negative pelvic ultrasound to assess its role in triaging treatment, access to specialist services and time to diagnosis and symptom control. We recommend a new treatment pathway for those women presenting to their family practitioner with pelvic pain or subfertility which promotes patients' autonomy, speed of diagnosis, and access to treatment or specialist advice.

4.6 CONCLUSION

In the absence of a more accurate, non-invasive diagnostic test, CA-125 $\geq$ 30 iu/ml can act as a rule-in test for women with pain or subfertility.

This chapter is based on the following publication:

Diagnostic accuracy of CA-125 for endometriosis in symptomatic women: A multi-center study.

Hirsch M, Duffy J, Deguara C, Davis C, Khan K.

Eur J Obstet Gynecol Reprod Biol. 2017 Mar;210:102-107.

CHAPTER 4:

VARIATION IN OUTCOME REPORTING IN ENDOMETRIOSIS TRIALS – A SYSTEMATIC REVIEW

In this chapter I will discuss the most commonly reported outcomes and outcome measures used in treatment effectiveness trials in endometriosis. I will describe their quality and associations with journal impact factor, methodological quality, year of publication, journal type and funding source.

5.1 ABSTRACT

Background: The reporting of outcomes within systematic reviews is dependent upon the quality and homogeneity of those reported within trials. Variation in outcome reporting leads to difficulty in comparing, contrasting and analysing data to generate clinical guidelines and improve patient care.

Objective: To reviewed the outcomes and outcome measures reported in randomised controlled trials (RCTs) of surgical interventions for endometriosis. To assess the relationship of the outcome quality with methodological quality, year of publication, commercial funding, and journal impact factor.

Data Sources: The following databases were searched from inception to November 2014: Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and MEDLINE

Methods of Study Selection: We included randomised controlled trials which evaluated a surgical intervention with or without an adjuvant medical therapy for the treatment of endometriosis. Two authors worked independently to select trials, assess methodological quality (Jadad score; range one to five), outcome reporting quality (MOMENT criteria; range one to six), year of publication, impact factor in the year of publication, and

presence or absence of commercial funding. Univariate and bivariate analysis were performed using both Spearman Rho and Mann-Whitney U tests. Multivariate linear regression models were used to assess the relationship associations between outcome reporting quality and other variables.

Results:

A total of 54 RCTs with 5427 participants reported 164 outcomes and 113 outcome measures. The three most reported primary outcomes were dysmenorrhea (10 outcome measures; 23 trials), dyspareunia (11 outcome measures; 21 trials), and pregnancy (3 outcome measures; 26 trials). The quality of outcome reporting was measured and the median score was 3 (interquartile range 4-2) and methodological quality 3 (interquartile range 5-2). Multivariate linear regression demonstrated a correlation between outcome reporting quality with methodological quality (β=0.325; p=0.038) and year of publication (β=0.067; p=0.040). No relationship was demonstrated between outcome reporting quality with journal impact factor (Rho=0.190; p=0.212) or commercial funding (p=0.370)

Conclusion: There is variation in outcome reporting within endometriosis trials. This prohibits comparison, combination, and synthesis of data, limiting the usefulness of research to inform clinical practice, enhance patient care, and improve patient outcomes. This demonstrates the need to generate an international consensus among stakeholders to standardise outcome reporting through the development of a core outcome set for endometriosis trials.

5.2 INTRODUCTION

Endometriosis is a common disease affecting 1 in 10 women impairing health related quality of life in the domains of fertility, pain, psychological, and social functioning. Endometriosis is a poorly understood disease and is managed with alternative, holistic, medical, and surgical therapies. There is currently no consensus amongst stakeholders (patients, healthcare professionals, and researchers) regarding the most important outcomes and outcome measures which should be collected and reported in endometriosis effectiveness trials. The factors leading to outcome reporting variation are unclear. Without stakeholder generated consensus, the variation in outcome reporting within effectiveness trials will continue to produce misleading results as these individual studies cannot be compared or combined. This can lead to the favouring of ineffective interventions or underestimating harms (324,325). The accurate measurement and reporting of consistent comparable outcomes is crucial to developing the highest level of evidence.

In line with a statement from the US Congress established Patient-Centered Outcomes Research Institute (PCORI) we hope that this review will help towards ensuring the selection of ‘‘outcomes that people in the population of interest notice and care about’’ (326).

In this chapter I aimed to systematically organise and describe the outcomes, their measurement instruments and definitions reported by RCTs evaluating surgical interventions for endometriosis. I assessed other publication features, such as journal impact factor, year of publication, methodological quality, and publication location (general or women’s health specific journal) are correlated to outcome reporting or methodological quality.

5.3 METHODS

A protocol with clearly defined objectives, criteria for study selection, and approaches assessing outcomes selection was developed. This study was prospectively registered with the Core Outcome Measures in Effectiveness Trials (COMET) (327) Initiative and reported in accordance with the PRISMA guidelines (328).

Sources

We searched CENTRAL, Embase, and Medline for relevant citations from database inception to November 2014 with no language restrictions. We reviewed the Cochrane Register of Systematic reviews to identify any additional systematic reviews then searching their bibliography for eligible trials (329).

Study Selection

Two independent reviewers (MH & JMND) screened titles and abstracts. The full text of selected studies were critically reviewed to assess eligibility by both MH & JMND. Discrepancies between the two reviewers were resolved by discussion with a more senior third author (KSK). We included only randomised control trials (RCTs) assessing the effectiveness of any surgical procedure with or without an adjuvant medical therapy for the treatment of endometriosis. We excluded, non-randomised, quasi-randomised, diagnostic and analytical studies.

Two reviewers (MH and JMND) extracted data independently using a piloted data extraction sheet. We extracted study characteristics including the publishing journal, setting, study design, sample size calculation, interventions, participants, and pharmaceutical funding. The study characteristics were summarised in tabular form (Table 8). We used the online platform, Researchgate, to assess the impact factor in the

year of publication. We systematically reviewed primary and secondary outcomes and their definitions and instruments.

Table 8 - *Study Characteristics*

Study	IF	Method. quality	Outcome quality	Intervention group one	Intervention group two	Intervention group three
Abbott 2004	3.17	5	4	Diagnostic laparoscopy + delayed surgical treatment	Surgical treatment + repeat surgery	
Abu Hashim 2012	1.85	5	6	Surgical treatment + superovualtion with letrozole + intrauterine inseminiation (IUI)	Surgical treatment + superovulation with clomiphene citrate + IUI	
Acien 2002	3.202	2	2	Surgical treatment + interferon α-2b	Surgical treatment + saline	
Alborzi 2004	3.17	2	5	Surgical treatment + ovarian fenestration and coagulation	Surgical treatment +ovarian cystectomy	
Alborzi	3.168	2	2	Surgical Treatment	Surgical treatment	Surgical treatment

2007				+ ovarian fenestration and coagulation	+ ovarian cystectomy	+ ovarian fenestration and cystectomy
Alborzi 2011	1.072	2	2	Surgical treatment + GnRHa	Surgical treatment + aromatase inhibitor	Surgical treatment
Alkatout 2013	1.575	2	2	Surgical treatment	HT	Surgical treatment + HT
Audebert 1998	0.745	2	2	Surgery treatment + GnRHa	GnRHa + Surgical treatment	
Ballester 2011	3.468	2	4	Laparoscopy + colorectal resection	Laparotomy + colorectal resection	
Beretta 1998	3.344	2	2	Surgical treatment + ovarian cystectomy	Surgical treatment + ovarian fenestration and coagulation	
Bianchi 1999	3.643	3	2	Surgical treatment	Surgical treatment	

				+ Danocrine		
Busacca 2001	2.751	3	2	Surgical treatment + GnRH agonist	Surgical treatment	
Candiani 1992	1.982	3	3	Surgical treatment + presacral neurectomy	Surgical treatment	
Cobellis 2011	1.974	5	3	Surgery treatment + Fatty acid amide	Surgical treatment + selective COX2 NSAID	Surgical treatment
Cosson 2002	3.202	3	4	Surgical treatment + Progestin	Surgical treatment + GnRHa	
Costello 2010	3.122	5	6	Surgical treatment + multimodal intraoperative analgesia	Surgical treatment + placebo	
Creus 2008	2.537	5	0	Surgical treatment + Xanthine derivative	Surgical treatment + placebo	

Darai 2010	7.474	3	5	Laparoscopy + colorectal resection	Laparotomy + colorectal resection
Darai 2011	3.564	3	2	Laparoscopy + colorectal resection	Laparotomy + colorectal resection
diZerega 2007	3.168	5	3	Surgical treatment + Adhesion barrier gel	Surgical treatment
Healey 2010	3.122	5	3	Surgical treatment + ablation	Surgical treatment + excision
Hoo 2014	3.483	5	6	Surgical treatment + ovarian suspension	Surgical treatment
Jarrell 2005	-	5	2	Surgical treatment	Diagnostic Laparoscopy + biopsy
Kamencic 2008	-	3	2	Surgical treatment	Surgical treatment

				+ Xanthine derivative	
Koninckx 2013	2.03	5	6	Surgical treatment + humidified CO2 pneumoperitoneum	Surgical treatment + peritoneal full conditioning and barrier gel
Lalchandani 2005	-	2	3	Diagnostic laparoscopy + GnRHa + HT	Sugical treatment + helium thermal coagulator
Loverro 2008	1.565	5	2	Surgical treatment + GnRHa	Surgical treatment + placebo
Mais 1995	-	2	5	Surgical treatment + adhesion barrier	Surgical treatment
Marcoux 1997	27.766	5	6	Surgical treatment + ablation	Surgical treatment + excision
Matorras 2002	3.202	2	2	Bilateral salpingo-oophrectomy + HT	Bilateral salpingo-oophrectomy

Moini 2012	0.471	5	4	Surgical treatment	Diagnostic Laparoscopy	
Morgante 1999	3.643	2	3	Surgical treatment + GnRHa + Danocrine	Surgical treatment + GnRHa	
Nowroozi 1987	-	3	1	Surgical treatment + ablation	Diagnostic Laparoscopy	
Parazzini 1994	2.247	5	3	Surgical treatment + GnRHa	Surgical treatment	
Parazzini 1999	3.643	3	2	Surgical treatment + ablation	Surgical treatment + excision	Diagnostic Laparoscopy
Seiler 1986	-	3	0	Surgical treatment + ablation	Treatment with Danocrine	
Soysal 2004	3.072	5	4	Surgical treatment + GnRHa	Surgical treatment + GnRHa + aromatase inhibitor	

Surrey 1994	-	2	3	Gamete Intra-fallopian tube transfer (GIFT) + Surgical treatment	GIFT	
Sutton 1994	2.464	5	3	Surgical treatment + presacral neurectomy	Diagnostic Laparoscopy	
Sutton 1997	2.612	4	2	Surgical treatment + presacral neurectomy	Diagnostic Laparoscopy	
Sutton 2001	0.63	5	2	Surgical treatment + presacral neurectomy	Surgical treatment	
Tanmahasamut 2012	4.798	5	5	Surgical treatment + Mirena IUS	Surgical treatment	
Telimaa 1988	-	4	1	Surgical treatment + Danocrine	Surgical treatment + progestin	Surgical treatment + placebo

Tsai 2004	0.778	5	2	Surgical treatment + GnRHa	Surgical treatment + Danocrine	Surgical treatment
Vercellini 1999	2.657	3	4	Surgical treatment + GnRHa	Surgical treatment	
Vercellini 2002	3.202	3	4	Surgical treatment + Progestin	Surgical treatment + COCP	
Vercellini 2003A	3.483	5	5	Surgical treatment + presacral neurectomy	Surgical treatment	
Vercellini 2003B	3.483	3	3	Surgical treatment + Mirena IUS	Surgical treatment	
Wickstrom 2012	4.542	5	3	Tubal pertubation + lidocaine	Tubal pertubation + placebo	
Wright 2005	3.114	4	2	Surgical treatment + ablation	Surgical treatment + excision	

Zhao 2013	1.401	1	2	Surgical treatment + chinese medicine	Surgical treatment + GnRHa + HT	Surgical treatment + progestin
Zhao 2013B	1.401	3	6	Surgical treatment + chinese medicine	Surgical treatment + GnRHa + HT	Surgical treatment + progestin
Zhu 2014	1.877	3	2	Surgical treatment + COCP	Surgical treatment + COCP + Chinese medicine	Surgical treatment
Zullo 2003	2.518	5	4	Surgical treatment + presacral neurectomy	Surgical treatment	

Quality Assessment

All included studies were assessed by two reviewers (MH and JD) independently evaluating each study's methodological and outcome reporting quality.

We used the internationally recognised JADAD criteria for assessment of methodological quality. The five point validated scoring system assesses the following: 1. Was the trial described as randomised? (1-point); 2. Did the trial use an appropriate method of randomisation? (1-point); 3. Was the trial blinded? (1-point), 4. Did the trial use an appropriate method of blinding? (1-point), 5. Did the trial account for all patients randomised? (1-point) (330).

Two reviewers (MH and JD) independently assessed each study's outcome reporting using the six point MOMENT scoring system which had been previously validated for the development of a core outcome set (331): 1. Was a primary outcome stated? (1-point), 2. Was the primary outcome clearly defined for reproducible measures? (1-point), 3. Were the secondary outcomes clearly stated? (1-pojnt), 4. Were the secondary outcomes clearly defined for reproducible measures? (1-point), 5. Do the authors explain the choice of outcome? (1-point), 6. Are the methods used designed to enhance quality of measures appropriate? (1-point). There is no well-defined rating score associated with this criteria, therefore a previously used cut off of ≥ 4 was used to represent ‘high’ quality trials (331).

Data synthesis

Non-parametric correlation coefficient (Spearman rho) was used to assess univariate association between continuous factors. The comparison of outcome reporting quality was assessed between groups according to funding source (commercial or other), year

of publication, type of journal (general vs. specialist), and impact factor in the year of publication. A specialist journal within obstetrics and gynaecology was defined by those found listed by www.scimagojr.com. Articles were reviewed closely for funding status. Those trials receiving commercial funding or the donation of equipment, which had facilitated the trial were classed pharmaceutically funded. The univariate analysis between non-continuous factors was performed using non-parametric Mann Whitney U tests. We used a multivariate linear regression model to assess the multivariate relationship of outcome reporting quality. We included journal type, impact factor in the year of publication, year of publication and methodological quality as independent variables and outcome reporting as the dependent variable. We only included significant predictors within the final model. We checked linear regression assumptions by exploring residuals versus predicted plot. The analyses were all performed using Stata program (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

5.4 RESULTS

The study selection is summarised in figure 14. There were 1570 titles and abstracts identified from the search strategy. We found 161 duplicate records, which we excluded, and screened 1409 titles and abstracts (figure 14). We included 54 RCTs (204,206,223,224,246–250,332–376) (Table 8). The included trials collected and reported 164 separate primary and secondary outcomes together with 113 outcome measures (Table 9). The outcome measurement or definition was not described within the trial report for 110 outcomes.

Outcomes were grouped by domain and the commonest outcome domains were pain 29/54 trials (53%), subfertility 22/54 trials (41%), and quality of life 9/54 trials (17%).

Figure 14 *- Flow of included studies.*

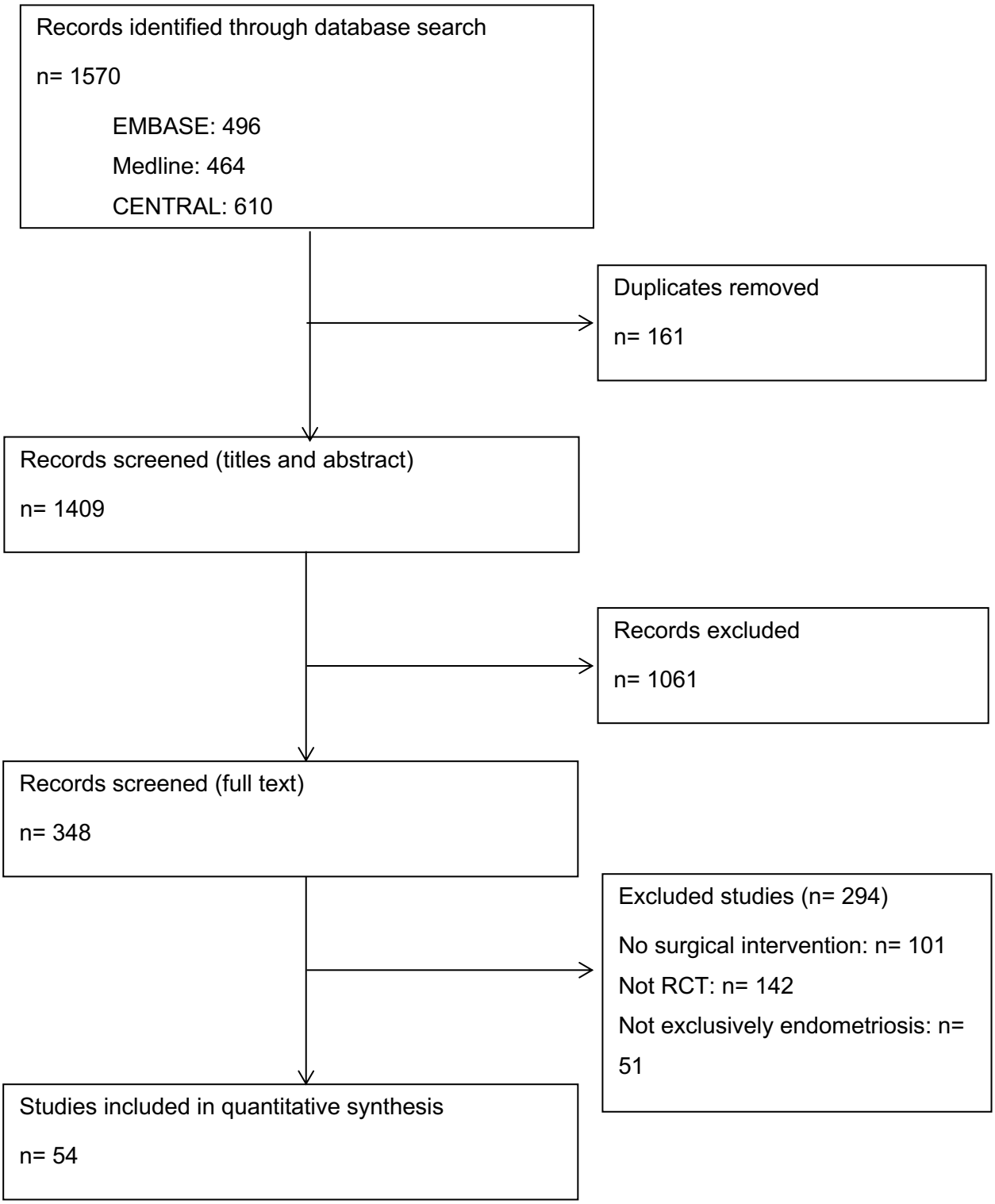


Table 9 - *Outcome and outcome measures reported*

Domain	RCTs	Outcomes*	Outcome measure*
Pain	37	32	24
Subfertility	32	28	11
Quality of life	9	10	10
Surgical adverse events	14	34	5
Medical adverse events	8	22	0

*Not an exhaustive list

Pain is a hallmark symptom of endometriosis and within the domain, the three most commonly reported outcomes were dysmenorrhea (23/54 RCTs, 10 outcome measures), dyspareunia (21/54 RCTs, 11 outcome measures), and pelvic pain (15/54 RCTs, 9 outcome measures). Three trials assessing pain did not specify the outcome measure used (337,347,348) (table 9, table 10, and table 11). Dysmenorrhea was measured with ten different outcome measures. Listed in order of frequency of use; visual analogue scale anchored between 0-10cm; visual analogue scale anchored between 0-100mm; visual analogue scale anchored between 0 (no pain) and 10 (severe pain); a visual analogue scale with no specified parameters; a questionnaire including three domains activities of daily living, coexistence of systemic symptoms, and analgesic requirement; a questionnaire with ranked symptoms; a questionnaire with no further description available; a ranked ordinal scale (1 to 5); number of episodes; and not specified.

Table 10 - *Reported pain and fertility outcomes*

Outcome domain	Outcome*	Trials (n)
Fertility outcomes	Pregnancy	26
	Miscarriage	7
	Live birth	5
	Estradiol	5
	Ectopic pregnancy	4
	Endometrial thickness	2
	Number of follicles >18mm	3
	Ampoules of gonadotropin	1
	Days of stimulation	1
	Early fetal loss	1
	Embryos per cycle	1
	Follicular Stimulating Hormone	1
	Luteinising Hormone	1
	Number of oocytes per cycle	1
	Pregnancy Interval	1
	Pregnancy subsequent cycle	1
	Reproductive outcome	1
	Singleton delivery	1
	Still birth	1
	Term delivery	2
	Twin delivery	1
	Twin pregnancy	1
	Vaginal delivery	1
Pain Outcomes	Dysmenorrhea	23
	Dyspareunia	21
	Pelvic pain	15
	Non-menstrual pelvic pain	6

	Dyschezia	6
	Overall pain	5
	Postop pain	3
	Abdominal pain	2
	Back Pain	2
	Aggregate pain	1
	Analgesia use	3
	Analgesic requirement	2
	Chest discomfort	1
	General Discomfort	1
	General pain	1
	Global intensity of pain	1
	Lateral menstrual pain	1
	Painless first stage of labor	1
	Postop opioid analgesia	1
	Rectal pain	1
	Shoulder pain	1
	Thigh pain	1
	Voiding pain	1

n= number of randomised trials reporting individual outcome measure.

*Not an exhaustive list

Table 11 - *Outcome measures for commonly reported outcomes*

Outcome	Outcome measure*	n
Dysmenorrhea	Visual analogue scale (0-10)	8
	Visual analogue scale (0-100)	7
	Visual analogue scale (0-10 with	3
	Visual analogue scale (no	1
	Ranked ordinal scale (1 to 5)	1
	Likert scale (0-10)	3
	Questionnaire (with description)	2
	Questionnaire (ranked symptoms)	1
	Questionnaire (no description)	1
	Number of episodes	1
	Not specified	2
Pregnancy	Serum βHCG	4
	Ultrasound (visualizing fetal heart)	4
	Ultrasound (growth scan)	2
	Pregnancy greater than 20 weeks	1
	Not specified	19
Quality of Life	World Health Organisation Quality	1
	EuroQol-5D	1
	Short Form Health Survey 12	1
	Short Form Health Survey 36	6
	Hospital Anxiety and Depression	2
	Greene Climateric Scale	1
	Blatt Kupperman Menopausal Index	1
	Sabbatsberg Sexual Rating Scale	1
	Revised Sabbatsberg Sexual	2
	Sexual Activity Questionnaire	1

n= number of randomised trials reporting individual outcome measure.

*Not an exhaustive list

Endometriosis is one of the largest causes for sub-fertility and is implicated as a cause in up to 50% of IVF cycles. The three most frequently reported fertility outcomes were pregnancy (26/54 RCTs, 5 outcome measures), miscarriage (7/54 RCTs, 2 outcome measures), and live birth (5/54 RCTs, 2 outcome measures). The following outcome measures were used to assess pregnancy in order of reducing frequency: serum beta HCG; ultrasound scan visualising fetal heart; ultrasound growth scan; pregnancy greater than 20 weeks gestation; not specified (table 11, figure 15).

Figure 15 -*Outcome reporting in Endometriosis trials: Largest 25 studies listed by study size showing pain and fertility outcomes.*

Study \ Outcome	Study size (n)	Pain									Fertility									
		Triad			Other						Pregnancy outcome							ART**		
		Dyschezia	Dysmenorrhoea	Dyspareunia	Overall pain	Abdominal pain	Shoulder pain	Pelvic pain*	Thigh pain	Postoperative pain	Pregnancy	Ectopic preganancy	Miscarriage	Twin pregnancy	Term delivery	Live birth	Still birth	Gonadotrophin use	Number of follicles	Embryos per cycle
Alkatout 2013	450		X	X		X					X	X	X		X					
Marcoux 1997	348										X	X								
Zhao 2013	320										X									
Vercellini 1999	269				X											X				
Vercellini 2003A	180		X	X				X			X									
Healey 2010	178	X	X	X	X	X		X	X											

Zhao 2013B	176																				
Matorras 2002	172																				
Zhu 2014	156		X	X	X					X		X	X				X				
Moini 2012	146										X										
Alborzi 2010	144		X	X				X			X										
Cosson 2002	142				X						X										
Zullo 2003	141		X	X				X													
Abu Hashim 2012	136										X		X	X		X		X	X		
Nowroozi 1987	123						X				X										
Creus 2008	104										X		X								
Parazzini 1999	101										X		X		X						
Alborzi 2004	100				X						X										
Vercellini 2002	90		X	X				X													
Seiler 1986	90										X										
Busacca 2001	89		X	X				X			X										

Alborzi 2007	88										X								X	
Soysal 2004	80																			
Bianchi 1999	77		X					X			X									
Parazzini 1994	75							X			X									
Other studies (29)	1452	5	14	14	0	0	0	13	0	2	9	1	2	0	0	3	0	0	1	1

*Pelvic pain - This includes non-menstrual pelvic pain

Endometriosis is associated with reduced quality of life and this outcome is the most highly predictive assessment tool for direct health care and total annual patient associated costs (101). Quality of life was reported by only nine of 54 RCTs using 10 different outcome measures including World Health Organisation Quality of Life-BREF; EuroQol-5D; Short Form Health Survey 12; Short Form Health Survey 36; Hospital Anxiety and Depression Scale; Greene Climacteric Scale; Blatt Kupperman Menopausal Index; Sabbatsberg Sexual Rating Scale; Revised Sabbatsberg Sexual Rating Scale; and Sexual Activity Questionnaire (204,338,347,348,367,370,371,374,376).

Intraoperative and postoperative complications were collected and reported by 14 RCTs using 34 different outcomes and 5 different outcome measures (223,249,334,342,344,347–349,351,354,355,357,359,375).

The mean outcome reporting quality was 3.15/6 (95% CI 1.65; 4.65) and methodological quality 3.61/5 (95% CI 2.35 - 4.88). Table 8 summarises quality assessment. Just over half of all trials clearly reported a primary outcome 32/54 (204,206,223,246–250,333,334,339,342,344,345,347–349,352,354,355,357,361,363,364,367,370–375) while just under half, 26/54 (204,206,246,248,249,332,341,342,345,347,348,350–352,355,357,361,366,367,369–371,373–376) described using a power calculation to influence their sample size. The majority of studies, 89% (n=48/54), were published in an obstetrics and gynaecology specific journal while 11% (n=6/54) trials were published in general medical journals including one trial in The New England Journal of Medicine (355). Studies receiving commercial or pharmaceutical funding accounted for 22% of trials (n=12/54)(223,248,249,337,345,346,350,355–357,367,373), while 4% of trials (n=2/54) (332,351) did not receive funding and 74% of trials (n=40) did not specify whether they received private funding (204,206,224,246,247,250,333–336,338–344,347–349,352–354,358–366,368–372,374–376).

We explored the relationship between quality of outcome reporting with impact factor in the year of publication, study quality, year of publication, journal type, and commercial funding (Table 12). After exploring the data we found one study (355) behaving clearly differently to the other studies in terms of impact factor (IF =27.776). This outlier was excluded from further analysis. Univariate analysis results are shown in Table 12. Year of publication and methodological quality of the paper correlated positively with quality of outcome reporting. Neither impact factor nor type of journal nor commercial funding was associated with outcome reporting. Multivariate analysis confirmed that both factors (year of publication and methodological quality) were independently associated with outcome reporting (Table 12). Residual plot did not show any evidence of violating assumptions of linear regression.

Table 12 -*Multiple linear regression analysis to determine factors associated with quality of outcome reporting*

Factor	Univariable		Multivariable*	
	Rho Spearman	**p**	**β**	**p**
Study quality+	0.379	0.010	0.325	0.038
Impact factor at publication	0.190	0.212	-	-
Journal type (specialist/generalist)**	-	0.691	-	-
Year of publication	0.294	0.050	0.067	0.040
Commercial funding**	-	0.370	-	-

+ Measurement details in methodology section

* Based on best sub-set regression

** Based on Mann-Whitney test

4.5 DISCUSSION

This chapter has found that there is outcome reporting heterogeneity in RCTs evaluating treatment effectiveness of surgical interventions for endometriosis. The commonest comparable outcome (dysmenorrhea) and its commonest measurement tool (visual analogue scale from 1-10) were used synonymously in only eight of 54 RCTs (15%).

There was a relationship demonstrated between the quality of outcomes reported and the methodological quality of a study and year of publication. There was no association seen with journal impact factor at publication in a multivariable analysis. It was difficult to produce meaningful comparisons relating to ethnicity as the RCTs included were conducted from an array of international settings with multiple patient populations.

The strengths of this prospectively registered review include its originality, robust search strategy and methodological design. This chapter describes the first systematic review of outcome reporting variation in endometriosis trials. The search was guided by the Cochrane Collaboration handbook in order to prevent bias in the review process. The selection and assessment of trials had good reviewer agreement, with discrepancies resolved quickly. This review, like others, has limitations we must acknowledge. We limited the inclusion of studies to only RCTs, this resulted in missing all those outcomes included in observational studies. The use of patient reported questionnaires to generate outcomes was widely employed within the included studies. These questionnaires introduce methodological inaccuracies as they are difficult to replicate, can lack reliability, and demonstrate varied sensitivity for the measurement of their desired outcome (377). This can lead to heterogeneity between disease or symptom endpoints. This subsequently results in an inability to compare the effectiveness of an intervention on a specified outcome (378).

Interpretation

There was a lack of association between journal impact factor and outcome reporting quality. This finding may suggest that journal editors prioritise those studies with sound methodological quality or favourable results ahead of outcome reporting quality. Alternatively, this could be the result of outcome reporting bias. This could involve the selection of 'cherry picked' attractive results for submission without negative or inconclusive results. However, this is difficult to prove or negate without a set of core outcomes.

The high prevalence of outcome reporting bias has been highlighted as a concern and can impact on Cochrane reviews (251). A review of outcome reporting bias within Cochrane reviews found that following adjusting for outcome reporting bias the treatments' effect estimate became non-significant in 19% of reviews and 26% of their reviews would have overestimated the treatment effect by greater than 20%. An analysis of research spending found that 85% of research funding is wasted across all aspects of the research cycle. Three of the four most common sources of waste were closely related to the reporting of outcomes: 1) important outcomes are not assessed, 2) published research fails to set the study in the context with all previous similar research and, 3) over 50% of planned study outcomes are not reported (379).

The All Trials initiative has looked to address this and, regardless of findings, all RCTs are published. The aims of this initiative is to eliminate publication bias from those studies that are withheld from publication where there is negative or no effect demonstrated (380).

The long term effect of outcome reporting variation is the restriction to produce meaningful conclusions. This limits the usefulness of research to inform clinical practice (381). Systematic reviews and meta-analyses are the highest quality research that can be used to implement evidenced based medicine, yet outcome reporting diversity

restricts the combination of results for meta-analysis. This is of particular concern to health economists as two thirds of the annual health related disease costs for patients with endometriosis (€9579) are attributed to loss of productivity (101). This is comparable to Crohns disease or Diabetes mellitus (101). Without harmonised outcomes the development of new, effective treatment modalities for women with endometriosis will not be achieved.

Recommendation(s)

The selection of pre-defined appropriate outcomes and outcome measures within endometriosis is necessary to limit bias and enhance patient centred care. The production and implementation of a core outcome set would help to address these concerns (382). A core outcome set is a collection of well-defined, discriminatory, and feasible outcomes that are the minimum measured endpoints to be reported by a trial or a systematic review. This does not restrict a trial or systematic review to the core outcome set however, it is envisaged that in most trials, the primary outcome would be selected from the core outcome set. The COMET Initiative was launched in January 2010. This aims to address the lack of standardised outcomes by aiding researchers with the prospective registration and development of core outcome sets.

Improving published research is supported by CoRe Outcomes in WomeN's health (CROWN) initiative, led by journal editors, this encourages and promotes the publication of studies which, where available, use outcomes from a published core outcome set. Implementing core outcome sets will augment and maintain the production of homogenous comparable data for improved evidence based patient care (382). The World Health Organisation, National Institutes of Health, and the Cochrane Collaboration have committed to supporting the development and implementation of core outcome sets.

This study demonstrates that reporting of outcomes following the surgical treatment of

endometriosis is inconsistent and requires standardisation. There is no internationally agreed selection of outcomes for trials and systematic reviews to evaluate. The development and use of core outcome sets routinely in the treatment of endometriosis will enable scientific summarising of outcomes from different studies and centres while reducing outcome reporting bias (251). In the absence of a core outcome set for endometriosis we recommend the use of the three commonest outcomes and their outcome measures. This will maximise the contribution of each individual trial to meta-analysis and clinical guideline development following trial completion (table 10 and table 11).

5.6 CONCLUSION

Variation in outcome reporting leads to multidirectional research that lacks comparability and threatens patient care. There is clear and evident need for the harmonisation of patient centered clinical outcomes through the development of a core outcome set in endometriosis.

This chapter is based on the following peer-reviewed publication:

Variation in Outcome Reporting in Endometriosis Trials: A Systematic Review.

Hirsch M, Duffy JM, Kusznir JO, Davis CJ, Plana MN, Khan KS.

Am J Obstet Gynecol. 2016 Jan 14. pii: S0002-9378(15)02587-9.

CHAPTER 5:

GOOGLING ENDOMETRIOSIS – A SYSTEMATIC REVIEW OF INFORMATION AVAILABLE ON THE INTERNET

6.1 ABSTRACT

Objective

We aim to evaluate the credibility, quality, readability, and accuracy of online patient information concerning endometriosis.

Data sources

We searched the five popular internet search engines: [1] aol.com; [2] ask.com; [3] bing.com; [4] google.com; and [5] yahoo.com. We developed a search strategy in consultation with patients with endometriosis, to identify relevant websites.

Website eligibility

Websites containing information related to endometriosis for women with endometriosis or the public.

Website appraisal and synthesis methods

Two independent authors screened the search results. Websites were evaluated using validated instruments across four domains, including assessments of: [1] credibility (White Paper instrument; range 0-10); [2] quality (DISCERN instrument; range 0-85); and [3] readability (Flesch-Kincaid instrument; range 0-100). Accuracy was assessed by a prioritised criteria developed in consultation with healthcare professionals, researchers, and women with endometriosis based upon the European Society of Human Reproduction of Endometriosis guidelines (range 0 – 30). We summarised these data in diagrams, tables, and narratively.

Results

We identified 750 websites, of which 54 were included. Over a third of websites did not attribute authorship and almost half the included websites did not report the sources of

information or academic references. No websites provided information assessed as being written in plain English. A minority of websites were assessed as high quality. A single website provided accurate information, evidentlycochrane.net. Available information was, in general, skewed towards the diagnosis of endometriosis. There were 16 credible websites, however the content limitations were infrequently discussed. No website scored highly across all four domains.

Comment

In the unlikely event that a website reports high quality, accurate, and credible health information it is typically challenging for a lay audience to comprehend. Healthcare professionals, and the wider community, should inform women with endometriosis of the risk of outdated, inaccurate, or even dangerous information online. The implementation of an Information Standard will incentivise providers of online information to establish and adhere to codes of conduct.

6.2 INTRODUCTION

Endometriosis is benign gynaecological disease which affects one in ten women of reproductive age, and is characterised by pain and subfertility with associated reduced quality of life (383). The economic burden of endometriosis is of a similar magnitude to other chronic diseases such as diabetes (101). There is a paucity of high quality research to guide clinical practice, this leads to unwarranted and unjustified variations in patient care (384).

The internet is fast becoming the preferred source of health information for patients who can access health information quickly, conveniently and privately. There are currently an estimated 6.75 million health searches daily in Google. This represents 4.5% of all searches performed (385). There has been a swift growth in the number of websites providing health information with little or no governance (386) while 7 in ten adults admit to regularly search for an explanation and information on a new diagnosis or treatment (387–389). Information provided online is commonly written at a high literacy level. This is further compounded by the difficulties patients may have establishing whether the information is accurate. The exposure to complex language, ungoverned, and unfounded health information could negatively affect patient understanding, compliance, and decision making. This could lead to poorer health outcomes, including harm (390–394). There are no systematic reviews assessing the quality of online patient information pertaining to endometriosis.

We systematically assessed the accuracy, quality, readability, and credibility of websites providing women with endometriosis and the public information regarding the diagnosis and management of endometriosis.

6.3 MATERIALS AND METHODS

Sources

A protocol with explicitly defined objectives, criteria for website selection, and approaches assessing outcome selection was developed and registered with the International PROSPERO, Identification number: CRD42016036134. This review was performed in accordance with the PRISMA statement (303).

Website Selection

We developed a comprehensive search strategy in consultation with healthcare professionals, researchers, and women with endometriosis. We used a keyword analytic instrument, SEMrush (www.semrush.com), to inform our selection of search terms. SEMrush provides analytical information related to search terms. We are confident we identified and selected all search terms commonly used by women with endometriosis. We used the following search terms: 1) endometriosis, 4,560,000 searches per annum; 2) endometriosis symptoms, 325,200 searches per annum; 3) endometriosis treatment, 64,800 searches per annum; 4) endometriosis pain, 19,200 searches per annum; and 5) endometriosis diagnosis, 15,600 searches per annum. We searched the most popular search engines including: 1) aol.com; 2) ask.com; 3) bing.com; 4) google.com; and 5) yahoo.com, during March 2016.

Individuals rarely examine more than the first three pages of a search (392). We therefore extracted the websites from the first three pages for each search term within each search engine. Location services were disabled to eliminate geographical bias.

We organised the extracted websites and removed duplicates. Two reviewers (M.H. and S.A.) independently screened the full content of websites to assess eligibility. All data extraction was performed using piloted data extraction instruments. We pilot tested each

instrument using a representative sample of the websites to be reviewed. This testing helped identify data that are missing from the form, or likely to be superfluous. This allows authors trialing the form to provide feedback that certain coding instructions are confusing or incomplete (e.g. a list of options may not cover all situations). Any discrepancies between the reviewers were resolved by discussion with a consensus required before the form is modified to avoid any misunderstandings or later disagreements. We repeated the pilot testing on a new set of websites where no major changes were needed after the first pilot testing (395).

We included websites providing health information about endometriosis greater than 300 words in length. We excluded websites for the following reasons; 1) non-English language; 2) inaccessible, for example password restricted; 3) aimed at a professional audience, for example scientific publication; 4) excessive commercial advertising (two or more commercial advertisements); and 5) content related solely to the lived experience of endometriosis, for example a patient's diary or blog.

Those websites which met the criteria for inclusion were saved as a portable document format for evaluation and data extraction by two independent authors (M.H & S.A). M.H. and J.D. did not assess any websites they had previously contributed too.

Website Characteristics

Two reviewers (M.H. and S.A.) extracted the website characteristics independently using a piloted data extraction sheet. Information extracted from each website included country of origin, disease specific information, listed authors, and privacy statements. Two reviewers (M.H. and S.A.) independently assessed each website using validated instruments including assessments of 1) credibility assessed using the White instrument (396) anchored between 0 (poor) and 10 (excellent) 2) quality assessed using the DISCERN (397) instrument anchored between 0 (poor) and 85 (excellent), and 3) readability assessed using the Flesch-Kincaid (398) instrument anchored between 0

(poor) and 100 (excellent). Discrepancies were resolved by discussion.

Quality Assessment

Two reviewers (MH and SA) underwent training in the use of the quality assessment instruments. We assessed accuracy using a prioritised list of recommendations included within the ESHRE endometriosis guidelines (107). The ESHRE guideline was selected for comparison as this was objectively assessed to represent the highest quality endometriosis guideline (399). All recommendations were extracted by two authors independently. Discrepancies were resolved by discussion. In consultation with healthcare professionals, researchers and women with endometriosis, the recommendations were scored as 1) critical for decision making, 2) important but not critical for decision making and 3) not critical and not important for decision making. Fifteen guideline recommendations were selected as statements critical for decision making (Appendix 2). The assessment of accuracy was standardised against selected guideline recommendations. This approach has been utilised in similar research studies (400).

Two reviewers (M.H and S.A) independently reviewed each website and using a piloted standardised proforma assessing the accuracy of information. Each recommendation was scored: 0 (if absent or incorrectly described), one (present and incompletely described), or two (present and completely described). Accuracy assessment was anchored between zero and 30. Discrepancies were resolved by discussion. We classified websites with a score greater than or equal to 20 as accurate.

The website's credibility was assessed by two reviewers independently using a validated instrument, White (396). This instrument, designed for consumers of health information, provides a set of criteria that can be used to accurately and reliably assess the quality of health information on the Internet. Credibility was assessed using a ten point criteria: 1) source; 2) context; 3) currency; 4) utility; 5) editorial review process; 6) hierarchy of

evidence; 7) statement of original source; 8) disclaimer, which included ownership, sponsorship, funding and advertising; 9) omissions; and 10) feedback. Each criterion was scored 0 (absent) or one (present) giving a score anchored between 0 to 10 (401). Discrepancies were resolved by discussion. We classified those websites with a score greater than or equal to seven as credible.

The website's quality was assessed by two reviewers independently using a validated instrument, DISCERN (397), a validated instrument designed to assess the quality of written information on treatment choices which can be applied to any disease (388,397). The DISCERN instrument offers a framework for the production, evaluation, and screening of written consumer health information. This includes 16 questions assessed using a Likert scale anchored between one (do not agree) and five (agree) (397). Discrepancies were resolved by discussion. We classified those websites as high (>53), moderate (27→52), and low (<27) quality.

The website's readability was assessed using the Flesch-Kincaid reading-ease test (398). This formula presents a score as a U.S. grade level, making it easier for teachers, parents, librarians, and consumers of health information to judge the readability level of various texts. The Flesch Kincaid score is generated from the following equation: 206.835 – 1.015 (total words / total sentences) – 84.6 (total syllables / total words) (www.readability-score.com) (398). The scores were anchored between 0 (complex language) and 100 (simple language) and can be categorised by reading age or educational status: 1) 90-100 (5th grade); 2) 80-90 (6th grade); 3) 70-80 (7th grade); 4) 60-70 (8th and 9th grade); 5) 50-60 (10th, 11th and 12th grade); 6) 30-50 (college); 7) 0-30 (college graduate). Discrepancies were resolved by discussion.

A large-scale national assessment of the average reading level among Americans performed by the National Center for Education Statistics found that the typical American reads between a 7th and 8th grade level (402). It is recommended that online health

information should not exceed the level of American 7th grade writing and reading (403). We therefore expected websites to have a readability score at or below the level of American education 7th Grade (>70) to be deemed appropriate for a patient and public audience.

Analysis

The website characteristics and assessments were summarised in tabular form and presented with descriptive statistics within summary tables and diagrams.

6.4 RESULTS

The search strategy identified 750 websites which were assessed for eligibility. We screened 211 websites following the exclusion of 539 duplicate websites. Two authors independently applied an inclusion and exclusion criteria when screening the websites. We included 54 websites in our final assessment (figure 16, Table 13).

Figure 16 - *Flow of included websites*

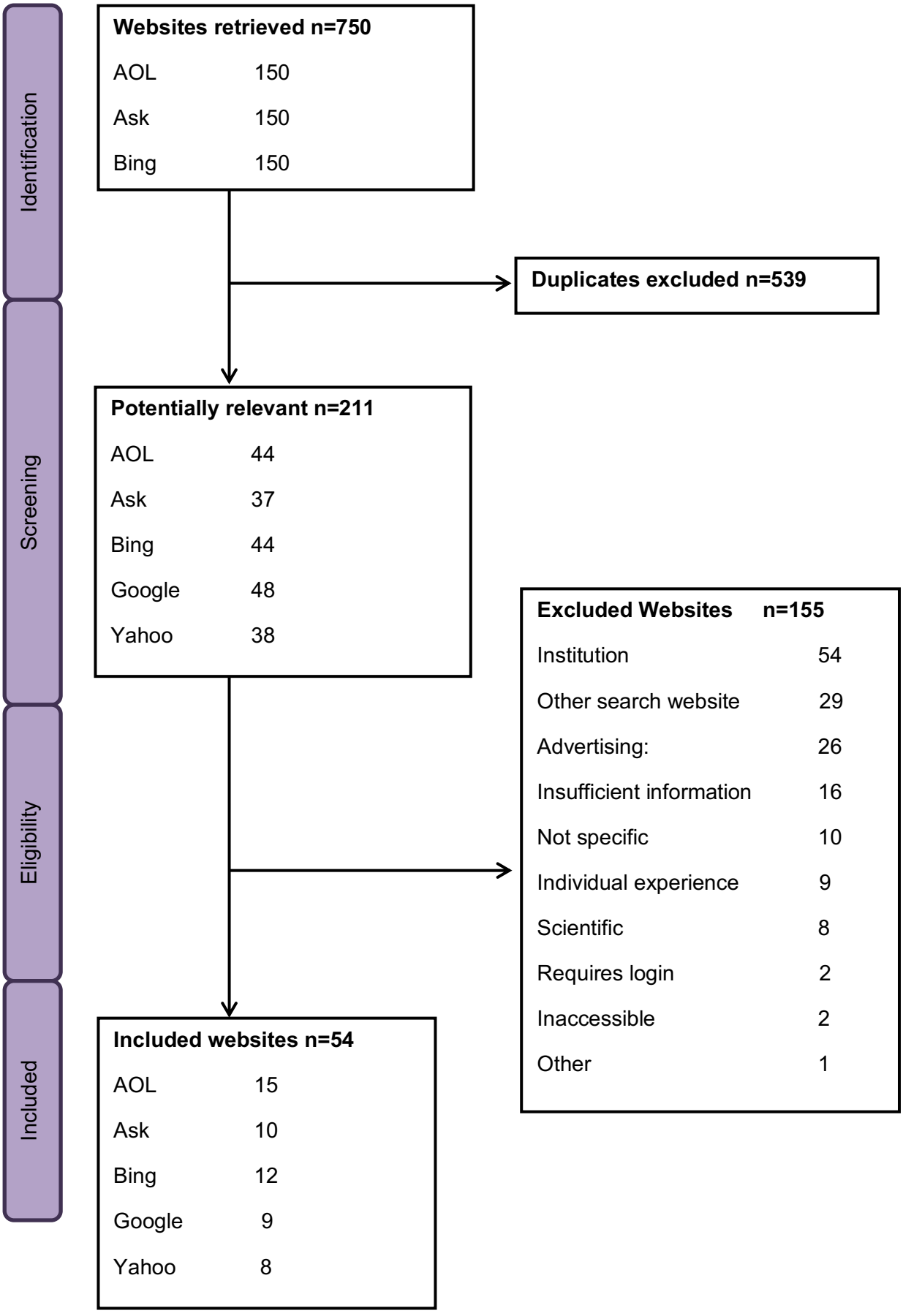


Table 13 - *Web site characteristics and a summary of quality, accuracy, credibility, and readability assessment*

I.D.	Web Domain	Country	Listed Authors	Privacy Statement	Quality	Accuracy	Credibility	Readability
1.	endocenter.org	USA	No	Yes	46	6	7	26.8
2.	endometriosis.org	Global	No	Yes	62	10	8	30.7
3.	endometriosis.org	Global	No	Yes	50	12	6	39
4.	endometriosis.org	Global	No	Yes	50	10	8	38.3
5.	endometriosis.org	Global	Yes	Yes	37	1	4	47.6
6.	endometriosis.org	Global	No	Yes	42	7	5	38.5
7.	home.bt.com	UK	Yes	Yes	46	5	5	38.2
8.	lifestyle.one	UK	Yes	No	48	4	5	52.3
9.	medical-dictionary.thefreedictionary.com	USA	No	Yes	62	10	8	24.3
10.	metro.co.uk	UK	Yes	No	37	2	3	61
11.	pain.about.com	USA	Yes	Yes	61	13	6	45.9
12.	patient.info	UK	Yes	No	69	10	9	48.1
13.	shetrust.org.uk	UK	No	No	35	2	4	23
14.	sogc.org	Canada	No	Yes	42	9	4	33.7
15.	womenshealth.about.com	USA	Yes	Yes	42	2	6	32.6
16.	activebeat.com	Canada	No	Yes	28	1	3	34.8
17.	babycentre.co.uk	Global	No	Yes	40	10	8	55.4
18.	channel4embarrassingillnesses.com	UK	No	Yes	32	2	5	49.8
19.	cwhn.ca/node/40781	Canada	No	No	43	4	3	38.5
20.	endo-resolved.com	UK	No	No	35	3	4	38.3
21.	endo-resolved.com	UK	No	No	37	2	4	32.2
22.	endo-resolved.com	UK	No	No	54	5	4	47.3
23.	endometriosis.ie	Ireland	No	Yes	39	10	4	23.5
24.	endometriosisaustralia.org	Australia	No	No	58	10	5	49.1
25.	endometriosisinstitute.com	USA	No	No	50	8	4	23

26.	endometriosisinstitute.com	USA	No	No	51	8	4	21.3
27.	evidentlycochrane.net	UK	Yes	No	45	4	7	29.6
28.	evidentlycochrane.net	UK	Yes	No	56	2	7	40.4
29.	healthline.com	USA	Yes	Yes	62	7	8	40.6
30.	hellomagazine.com	UK	No	Yes	38	3	4	51.7
31.	independent.co.uk	UK	Yes	Yes	32	4	5	46.3
32.	livescience.com	Global	Yes	Yes	47	6	3	34.9
33.	medicalnewstoday.com	UK	Yes	Yes	45	2	8	24.8
34.	netmums.com	UK	No	No	45	5	4	28.1
35.	nytimes.com	USA	Yes	Yes	51	5	8	57
36.	nzendo.org.nz	New Zealand	No	No	40	6	4	34.2
37.	pelvicpain.org.uk	UK	No	Yes	57	11	8	21.5
38.	pelvicpain.org.uk	UK	No	Yes	38	6	5	33.6
39.	prevention.com	USA	Yes	Yes	35	3	4	32.8
40.	students4bestevidence.net	UK	Yes	Yes	47	28	7	5
41.	theguardian.com	UK	Yes	Yes	40	6	3	56.8
42.	theguardian.com	UK	Yes	Yes	31	5	4	53.4
43.	uptodate.com	UK	Yes	Yes	64	13	9	33.8
44.	womens-health.co.uk	New Zealand	No	Yes	22	3	3	38.1
45.	womens-health.co.uk	New Zealand	No	Yes	35	5	2	49.3
46.	youngwomenshealth.org	USA	Yes	No	61	4	4	55.1
47.	en.wikipedia.org	Global	No	Yes	50	11	8	23.9
48.	health.facty.com	Canada	Yes	Yes	32	1	5	44.9
49.	betterhealth.vic.gov.au	Australia	No	Yes	61	8	7	30.8
50.	endometriosis-uk.org	UK	No	Yes	42	2	5	31
51.	endometriosis-uk.org	UK	No	Yes	40	1	5	24.8
52.	endometriosis-uk.org	UK	No	Yes	41	2	5	32
53.	endometriosis-uk.org	UK	No	Yes	53	0	5	51.6
54.	endometriosis-uk.org	UK	No	Yes	33	2	5	48.3
	Median				44	5	5	38.2
	IQR				(37–51)	(4-7)	(2–9)	(30–48)

[a]DISCERN tool to assess quality of information (range 16 - 80)
[b]Accuracy assessed using selected criteria from 2013 ESHRE guidelines (range 0 - 30)
[c]Credibility based on ten criteria (range 0 - 10)
[d]Readability assessed using the Flesch Reading Ease tool (range 0 - 100)

Website characteristics

Twenty-one (39%) websites did not report the authors and 25 (46%) of websites did not report sources of information or academic references. The majority of included websites were published in the United Kingdom (25 websites; 46%). All websites presented structured content. Almost two thirds of the websites reported a privacy statement (38 websites; 70%) (Table 13).

Accuracy

A single website provided accurate information, *evidentlycochrane.net*. The median accuracy of included websites was 5 (Interquartile range [IQR] 4 – 7). Included websites contained limited information (Table 13), skewed towards the diagnosis of endometriosis. Information pertaining to the medical or surgical management of pain or infertility associated with endometriosis were poorly represented. The most commonly reported recommendation, "*Clinicians should consider the diagnosis of endometriosis in the presence of gynaecological symptoms such as: dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility, fatigue in the presence of any of the above*", was described by four fifths of included websites (43 websites, 80%). The least frequently described recommendations, described by a small minority of included websites (3 websites; 6%) were: 1) "*In infertile women with endometriosis, clinicians may offer treatment with assisted reproductive technologies after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/* Intra-cytoplasmic sperm injection *(ICSI).*" 2) "*Clinicians [should] inform women with endometriosis requesting information on their risk of developing cancer that 1) there is*

no evidence that endometriosis causes cancer, 2) there is no increase in overall incidence of cancer in women with endometriosis, and 3) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis". The delivery of inaccurate, outdated or dangerous information remains prevalent in websites. Inaccuracies include: 1) "Your specialist may also suggest flushing out your blocked fallopian tubes. This procedure is an alternative to surgery and is usually successful" website ID 1. Routine tubal flushing is used in diagnostic evaluation of tubal patency and it is not recommended therapeutic approach (404). 2) "The only reliable way to confirm the presence of the disease is by visually inspecting the abdominal organs by a procedure called a laparoscopy" Website ID 20. There are many difficulties associated with visually confirming endometriosis. The most reliable way to diagnose endometriosis is laparoscopy, biopsy and histopathological examination. Visual diagnosis is no longer recommended (107). 3) "It is suspected that between 10-20% of reproductive aged women have the disease." Website ID 20. The estimated prevalence within the general population is up to 10% (107).

Credibility

Credibility was defined as a score equal to or greater than seven. Sixteen websites (29%) were assessed as credible. The median credibility of included websites was 5 (IQR 2 - 8.8). The highest scoring criteria included context relevant to the disease and originality with all websites fulfilling these criteria. The least frequently described area of credibility was the discussion of content limitations which was reported by one website (Table 13).

Quality assessment

Thirteen websites (24%) were assessed to be high quality, 40 (74%) websites were assessed to be of moderate quality, and a single website (2%) was assessed as low quality. The highest scoring criteria included describing aims (median = 5; IQR 3-4) and

being unbiased (median 5; IQR 4-5). Websites typically did not describe the consequences of no treatment (median 1; IQR 1-1).

Readability

All included websites were assessed as fairly difficult to read (10th, 11th, and 12th grade), difficult to read (college), or very difficult to read (college graduate). The median readability score was 38.2 (IQR 30.7 – 48.0), indicating an average educational status of a college student would be required to understand the written content (Table 13 and table 14). Forty-five websites (83%) presented written information at a level at or above college standard.

There were no substantial discrepancies between authors in the data extraction of quantitative parameters and we observed very high interrater agreement.

Table 14 - *Readability*

Ease of reading	USA educational level	Webpages (n)
Very easy to read (score 90-100)	5th Grade	0
Easy to read (score 80-90)	6th Grade	0
Fairly easy to read (score 70-80)	7th Grade	0
Plain English (score 60-70)	8th-9th Grade	1
Fairly difficult to read (score 50-60)	10th-12th Grade	8
Difficult to read (score 30-50)	College	32
Very difficult to read (score 0-30)	College Graduate	13

6.5 DISCUSSION

Summary

There are no websites which provide high quality, accurate, and credible health information pertaining to endometriosis. Currently, websites contain limited amounts of information which are skewed towards the diagnosis of endometriosis. In the unlikely event that a website reports high quality, accurate, and credible health information, it is typically written in language that is challenging for a lay audience to comprehend.

Strengths and Weaknesses

To our knowledge, this is the first study to examine the quality, credibility, accuracy, and readability of patient focused online information pertaining to the diagnosis and management of endometriosis. We followed a robust, prospective systematic review method with validated instruments to assess the information presented. We evaluated individual websites using four validated instruments in a systematic process, independently performing all assessments in duplicate. We involved women with endometriosis, to inform the research question, design and delivery of the research study, and its dissemination. All reviewers underwent recommended training prior to commencing the study.

This study is not without limitations. Limiting the search to the first three pages may have resulted in the exclusion of potentially eligible websites, however only 2.6% of people search past Googles' third page (www.protofuse.com). Included websites were only written in English language, limiting the generalisability of our findings. The search was conducted while computer location services were disabled, however there may have been regional differences in search results, out of the authors control, which account for the predominance of British websites. We designed and registered this systematic review prospectively with a pre-defined inclusion criteria and analysis plan. There are

few scientific publications which evaluate online information for patients allowing limited precedent to guide our methods. We observed diminishing returns, however this was not quantified. All websites were designed and managed within high resource countries. This limits the applicability of this research to inform low resource settings. We did not calculate weighted kappa to explore agreement between authors as the statistical level of agreement required in health research is unclear (405). This evaluation is not currently recommended by the Cochrane Collaboration (395). We could have conducted in-depth qualitative interviews of women with endometriosis to explore their satisfaction with reading individual websites and evaluate the correlation with accuracy, credibility, quality and readability.

Interpretation

As clinicians we must be aware that patients are increasingly seeking unregulated health information online which shapes opinions and treatment choices. The essence of modern clinical consultations is changing from a reliance on face-to-face interaction to information gathering online prior to seeking professional opinion. In the United States of America, there are over 400,000 endometriosis searches per month in Google alone. We have demonstrated that individual websites are frequently incomplete, inaccurate, and poorly written. This is a barrier to patient education and results in those vulnerable patients who seek reliable information being misinformed. This is of greater importance to non-expert patients (majority) who may be less able to evaluate the reliability of online information and be susceptible to the bias and inaccuracies contained within. These forays into online information gathering can lead to a breakdown in doctor patient relationships. Inaccurate online health information can lead to clinicians advocating guideline-supported recommendations different from those read on “reputable” online sources. This mismatch of information can lead to a breakdown in trust in the clinician-patient relationship.

A review conducted by the United States Office of Disease Prevention and Health Promotion (ODPHP) concluded that the potential for harm from inaccurate online information is significant (406). Harm can be: 1) physical, from inappropriate treatments, adverse effects, or untreated disease; 2) emotional, from anxiety or false hope arising from inaccurate diagnostic, prognostic, or therapeutic information; 3) financial, costs incurred from unnecessary purchase of ineffective health services or products (406). The ODPHP concluded that the Internet is critical to disease prevention, health promotion, and health care because of the increasing amount of information and services available via the internet. This included a key objective to increase the quality of online health information (407).

The readability of a website is an essential facet of online information. Information presented at a standard above patients' comprehension will limit its ability to inform the patient. Healthcare professionals should be aware that there is very limited information available to women with endometriosis with basic levels of literacy (indicates skills necessary to perform simple and everyday literacy activities), and therefore directing them to online information is of limited value in informing decision making.

Many online information rating systems use proxy markers for quality that do not consider the needs and opinions of patients and the public. Meric and colleagues (408), determined website popularity did not correlate well with traditional standards of website quality. Quality of online information is crucial as patients want to know about the risks, benefits, and uncertainty associated with diagnostic and therapeutic options. This information must be accurate to ensure that patients seeking information are gaining correct and complete information about the disease from up to date scientific evidence. Without access to good quality information, patients are unable to make informed choices about their treatment.

Recommendation(s)

Healthcare professionals and the wider medical community are increasingly quizzed by patients regarding health information found online. It is essential that healthcare professionals acknowledge their position of responsibility and proactively inform women with endometriosis about the risk of outdated, inaccurate, or even dangerous information online. Interactive consultations using online clinical practice guidelines such as those produced by the American College of Obstetrics and Gynecology (409) or the Society of Obstetricians and Gynaecologists of Canada (SOGC) (410) can provide the basis for clear, concise, evidence based management discussions. Following consultations, patients should be sign posted towards higher quality and more reliable sources of online information to answer questions they may have forgotten to ask during their limited consultation time.

While it may sound unrealistic to regulate health information on the internet, codes of conduct have been developed and implemented. The Health on the Net Foundation, based in the United States, provides accreditation to websites, which meet pre-defined standards related to readability, accessibility, and accuracy (398). The Information Standard, based in the United Kingdom, assesses online health information to ensure the information is clear, accurate, balanced, evidence-based, and up-to-date. Information produced by the Royal College of Obstetricians and Gynaecologists is accredited by this information standard (https://www.england.nhs.uk/tis/).

We acknowledge that regulating health information on the internet has inherent difficulties as online authors are not bound by the same codes of practice as licensed healthcare professionals. The implementation of a robust Information Standard internationally will incentivise providers of online information to establish and adhere to codes of conduct ensuring an improvement in the quality of online information. Healthcare professionals and professional bodies should direct women with endometriosis towards higher quality, more reliable sources of online information. In general, websites who comply with an Information Standard, should be prioritised.

The internet will continue to increase its role as a provider of online health information. The media by which health information is transferred from source to patient should not compromise the fundamental features of accuracy, credibility, quality and readability. It would not be tolerated if a healthcare professional were delivering sub-standard information in a face-to-face consultation. A strategy is required to improve the standard of online information for women with endometriosis with evident need for the development of patient focused online information with a robust evidence base. The translation of research from trials or systematic reviews into online sources has a direct pathway currently being delivered by Cochrane in the form of Evidently Cochrane summaries. These webpages summarise Cochrane systematic reviews into patient focused bite size pieces of information (411).

6.6 CONCLUSION

In the unlikely event that a website reports high quality, accurate, and credible health information it is typically challenging for a lay audience to comprehend. Healthcare professionals, and the wider community, should inform women with endometriosis of the risk of outdated, inaccurate, or even dangerous information online. Providers of online information should engage with established codes of conduct, such as the Information Standard.

This chapter is based on the following peer reviewed publication:

Hirsch M, Aggarwal S, Barker C, Davis CJ, Duffy JM. Googling endometriosis: a systematic review of information available on the Internet. Am J Obstet Gynecol. 2016 Nov 11. pii: S0002-9378(16)31987-1.

CHAPTER 6:

DIAGNOSIS AND MANAGEMENT OF ENDOMETRIOSIS: A SYSTEMATIC REVIEW OF INTERNATIONAL AND NATIONAL GUIDELINES.

7.1 ABSTRACT

Objective

We evaluated the methodological quality of endometriosis guidelines, mapped their recommendations, and explored the relationships between recommendations and research evidence.

Data Sources

We searched: [1] EMBASE; [2] Medline; and [3] Pubmed from inception to February 2016.

Methods of guideline selection

We included guidelines related to the diagnosis and management of endometriosis. Four independent authors assessed the methodological quality of included guidelines using the Appraisal of Guidelines for REsearch & Evaluation (AGREE-II) instrument and systematically extracted the guideline recommendations and supporting research evidence.

Tabulation, Integration, and Results

The search strategy identified 1879 titles and abstracts. We include two international and five national guidelines. No guideline followed the standardised guideline development methods (AGREE-II). Guidelines performed poorly in the domains of stakeholder involvement and rigor of development and very poorly in the domains of applicability and editorial independence. The ESHRE guideline was objectively evaluated as the highest quality guideline (methodological quality score: 88/100). One hundred and fifty-two different recommendations were made, 10 (7%) recommendations were comparable across guidelines. There was substantial variation between the supporting evidence

presented by individual guidelines for comparable recommendations. Forty-two (27%) recommendations were not supported by research evidence or cited expert opinion.

Conclusion

There is substantial variation in the methodological quality of endometriosis guidelines. Future guidelines should be developed with reference to high quality methods, in consultation with key stakeholders, including women with endometriosis, ensuring their scope can truly inform clinical practice and eliminate unwarranted and unjustified variation in clinical practice.

7.2 INTRODUCTION

Endometriosis is a common benign gynaecological disease characterised by pain and subfertility with substantial reductions in quality of life (106). The disease has three common manifestations: [1] peritoneal endometriosis; [2] ovarian endometriosis; and [3] DIE. The disease was first described in 1860 yet the etiology and pathogenesis remain poorly understood (91).Treatment strategies vary significantly between disease severity and presenting symptoms of pain and / or subfertility (412). These challenges have resulted in difficulties producing accurate diagnostic tests or effective therapeutic interventions.

Guidelines are systematically developed statements based upon research evidence (413).Their purpose is to improve patient care by informing clinical practice, reducing unwarranted variations in care, expediting the implementation of effective interventions, and eliminating ineffective interventions (414,415). The generation of robust guideline recommendations requires standardised guideline development methodology informed by evidence synthesis, including: [1] consensus method; [2] stakeholder engagement; and [3] quality assessment of research evidence. The methodological quality of guidelines has been reported to be inconsistent (416–418). Appropriate methodologies and rigorous strategies in the guideline development process are important for the successful implementation of the guideline recommendations (419,420). Previous comparisons of national endometriosis guidelines were limited by scope, setting, and did not map recommendations and supporting evidence across individual guidelines (421).

We evaluated the methodological quality of endometriosis guidelines, mapped their recommendations, and explored the relationships between recommendations and research evidence.

7.3 SOURCES

A protocol with explicitly defined objectives, criteria for guideline selection, and approaches assessing outcome selection was developed and registered with the International PROSPERO (CRD42016036145). This review is reported in accordance with the PRISMA statement (328). Search terms were generated in consultation with healthcare professionals, researchers, and women with endometriosis. We searched the following sources: [1] EMBASE; [2] Google; [3] Medline; and [4] PubMed from inception to February 2016 (figure 17). We used the following search terms: [1] endometriosis; [2] endometrio*; [3] guideline; [4] guidance; and [5] consensus.

Figure 17 - *Medline search strategy*

Search terms	Number of citations
endometriosis.ti,ab	17872
endometrio*.ti,ab	23895
guideline.ti,ab	33770
guidance.ti,ab	74046
consensus.ti,ab	116903
1 OR 2	23895
3 OR 4 OR 5	219169
6 AND 7	217

Selection Criteria

We organised the extracted guidelines and removed duplicates. Two reviewers (M.B. and M.H.) independently screened the full content of guidelines to assess eligibility, using a piloted data extraction tool. Any discrepancies between the reviewers were resolved by discussion. We included guidelines reporting recommendations for practice related to the diagnosis or management of endometriosis. Full text documents were selected for inclusion if they met the following criteria; [1] document type: guideline, consensus statement, healthcare technology assessment, produced by an international or national professional organisation; [2] subject: diagnosis and / or management of endometriosis published in English. We excluded guidelines for the following reasons: [1] local or regional guideline; [2] non-English language; and [3] more recent guideline available from the same authority.

Guideline Characteristics

Two reviewers (M.B, and M.H.) extracted guideline characteristics independently using a pilot tested data extraction sheet. During the piloting stage, authors were asked to provide feedback with regards to the form layout and instructions. No significant changes were needed following the pilot testing (395).

Information extracted included country of origin, year of publication, consensus method, stakeholders involved, disease area examined, description of database search, search terms used, language restriction, dates of searches, inclusion / exclusion criteria use, and quality assessment instrument use.

Assessment of Methodological Quality

Four reviewers (M.B, J.D, M.H, and E.P.) underwent training in the use of the quality assessment instrument, Appraisal of Guidelines for REsearch & Evaluation II (AGREE-II)

(422). Each reviewer independently assessed the quality of all included guidelines using the AGREE-II instrument. This validated assessment instrument contains 23 items grouped into six quality domains with a 7-point Likert scale score anchored between 1 (strongly disagree) and 7 (strongly agree) for each item. The AGREE-II instrument is divided in to six domains: [1] Scope and purpose (items 1–3); [2] Stakeholder involvement (items 4–7); [3] Rigor of development (items 8–14); [4] Clarity and presentation (items 15–18); [5] Applicability (items 19–21); and [6] Editorial independence (items 22–23) (422). Each appraiser allocated a score between 1 and 7 for each item, and a total domain score was calculated (422).

In addition, we assessed each guideline against six features of systematic review methodology (395); [1] named database search; [2] clearly defined search terms; [3] language restrictions; [4] dates of search; [5] detailed search strategy; and [6] description of an inclusion / exclusion criteria. Discrepancies were resolved by discussion (422).

Recommendations for Clinical Practice and Supporting Research Evidence

Two authors (M.B. and M.H) extracted guideline recommendations and their supporting references independently. We mapped the recommendation to five pre-specified domains: [1] diagnosis; [2] medical management for pain; [3] surgical management for pain; [4] medical management for infertility; and [5] surgical management of infertility. References supporting clinical recommendations were retrieved and categorised according to hierarchy of medical evidence: [1] Cochrane review; [2] systematic review; [3] randomised control trial; [4] non-randomised control trial; [5] expert opinion; and [6] no reference. Discrepancies were resolved by discussion.

Analysis

A total domain score for the AGREE-II instrument was calculated by summation of its items and standardised using the prescribed equation: [(obtained score – minimum possible score)/ (maximum possible score – minimum possible score)] x 100, where

maximum possible score was 7 (strongly agree) x number of items x 4 (number of appraisers), and minimum possible score was 1 (strongly disagree) x number of items x 4 (number of appraisers). This provides a quality score anchored between 0 and 100% for each of the six domains. We categorised guidelines in to poor quality (0-33%), moderate quality (34-66%), high quality (67- 100%). This was chosen as the most appropriate categorisation following discussion amongst the authors.

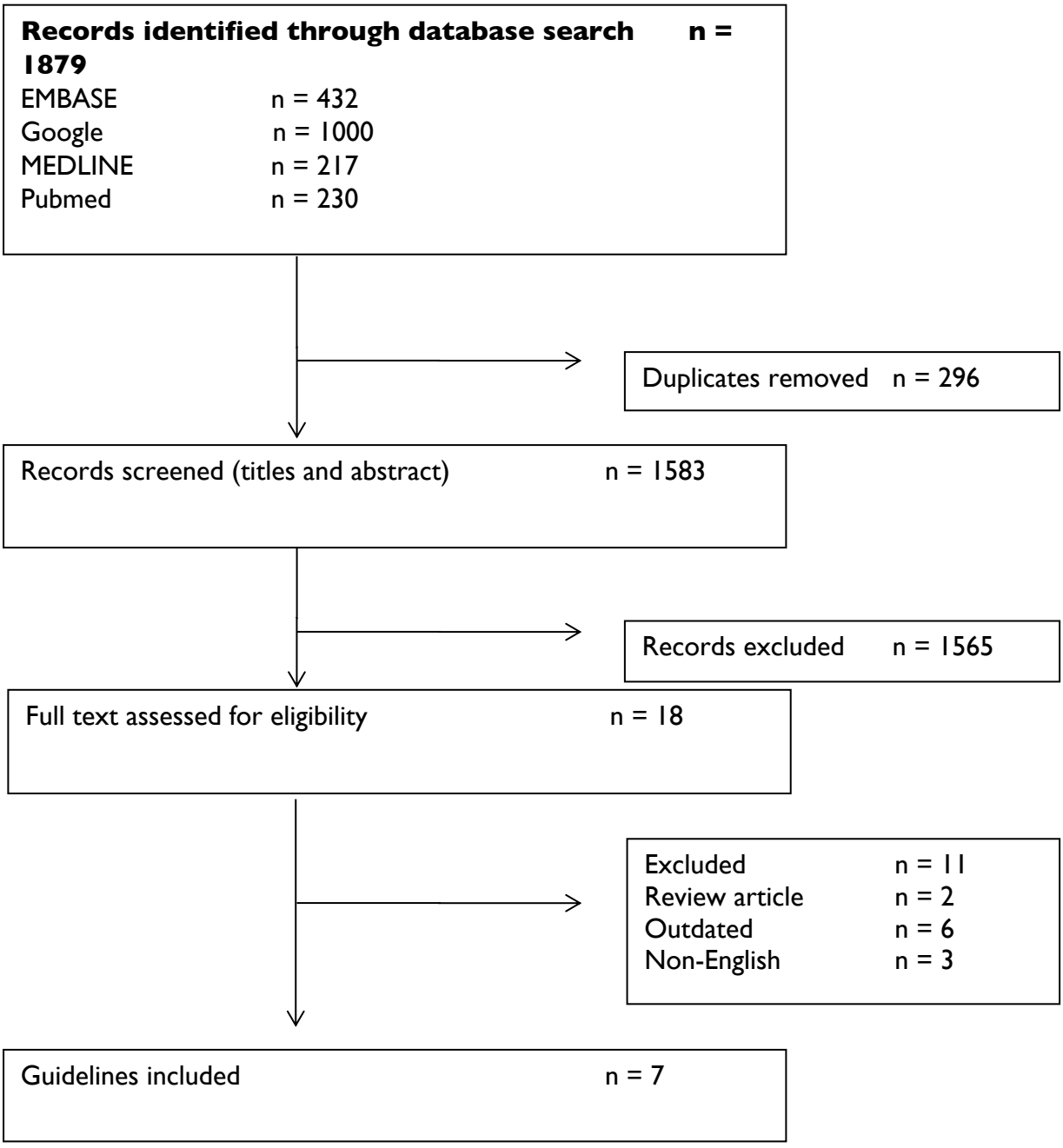
Tabulation and data

Descriptive statistics were calculated for all domains (median, range, IQR). We mapped the data for clinical recommendations, their supporting research evidence, and variation in clinical recommendations. There were no substantial discrepancies between authors in the data extraction of quantitative parameters and we observed high interrater agreement.

Guideline search and selection

The search strategy identified 1879 titles and abstracts. We screened 1583 titles and abstracts following the exclusion of 296 duplicate records (figure 18). We included the following two international (107,423) and five national (410,424–427) guidelines: [1] ACOG (424); [2] *Australasian Certificate of Reproductive Endocrinology and Infertility Consensus Expert Panel on Trial Evidence* (ACCEPT) (425); [3] *Collége National des Gynécologues et Obstétriciens Français* (CNGOF) *Guidelines for the Management of Endometriosis* (410); [4] (ESHRE) *Management of women with endometriosis* (107); [5] *National German Guideline (S2k) Guideline for the Diagnosis and Treatment of Endometriosis* (NGG) (426); [6] *SOGC* (427); and [7] *WES Consensus on current management of endometriosis* (423).

Figure 18 - *Flow of included guidelines.*



Guideline characteristics

The selected guidelines were published between 2006 (410) and 2014 (107,426). Five of the guidelines were applicable to the diagnosis and management of pain and subfertility associated with endometriosis (107,410,426,427). Two guidelines had narrower scopes: the *Australasian Certificate of Reproductive Endocrinology and Infertility Consensus Expert Panel on Trial Evidence* (ACCEPT) guideline addresses the management of subfertility associated with endometriosis (425); and the WES guideline addresses the management of pain and subfertility associated with endometriosis (423).

Between 15 (107) to 56 (423) individuals were involved in guideline development. Between one and four different stakeholder groups assisted in developing the included guidelines. Three guidelines were developed in collaboration with women with endometriosis (107,423,426). Two guidelines did not report the geographical location of their developers (410,424) and one guideline was developed by individuals living in a single country (427). All guidelines made recommendations relevant to high-resource settings only (311). Two guidelines explicitly defined a consensus development method, including the nominal group technique and modified Delphi method (107,425). No guideline described a detailed search strategy to identify evidence for use in recommendation formation. Five guidelines described methods to quality assess the evidence retrieved from their search strategy (107,423–425,427). We summarised guideline characteristics in table 15.

Table 15 - *Guideline Characteristics*

Guideline (year)	Scope	Stakeholders (n; location)	Consensus method	Identification of evidence	Quality assessment of evidence
ACCEPT (2012) (425)	[1] Infertility management [2] Pain management	[1] Healthcare professionals (36; unclear) [2] Women with endometriosis (unclear) [3] Pharmaceutical employees (unclear) [4] Researchers (unclear)	[1] Nominal group technique	Database: [1] Embase [2] Pubmed Search terms: reported Language: English Dates: not reported Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	National Health and Medical Research Council
ACOG (2010) (424)	[1] Infertility management [2] Pain management	Not reported	Not reported	Database: [1] ACOG [2] CENTRAL [3] Medline Search terms: not reported Language: English Dates: 1985 - 2010 Detailed search strategy: not reported	United States Preventative Services Task Force

				Inclusion / exclusion criteria: unclear	
CNGOF (2006) (410)	[1] Diagnosis [2] Infertility management [3] Pain management	Not reported	Not reported	Database: not reported Search terms: not reported Language: not reported Dates: not reported Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	Not reported
EHSRE (2014) (107)	[1] Diagnosis [2] Infertility management [3] Pain management	[1] Healthcare professionals (unclear) [2] Women with endometriosis (1; one country) [3] Pharmaceutical employees (unclear) [4] Researchers (n=14; Europe; nine countries)	[1] Nominal group technique [2] Modified Delphi method	Database: [1] CENTRAL [2] Pubmed Search terms: not reported Language: not reported Dates: Inception –January 2012 Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

NGG (2014) (426)	[1] Diagnosis [2] Infertility management [3] Pain management	[1] Healthcare professionals (11; unclear) [2] Women with endometriosis (unclear) [3] Pharmaceutical employees (unclear) [4] Researchers (21; Europe; five countries)	Not reported	Database: 1] CENTRAL [2] Medline [3] Pubmed Search terms: not reported Language: not reported Dates: not reported Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	Not reported
SOGC (2010) (427)	[1] Infertility management [2] Pain management	[1] Healthcare professionals (unclear) [2] Women with endometriosis (unclear) [3] Pharmaceutical employees (unclear) [4] Researchers (20; Canada)	Not reported	Database: [1] CENTRAL [2] Medline Search terms: not reported Language: English Dates: 1985 - 2010 Detailed search strategy: not reported Inclusion /exclusion criteria: not reported	Canadian Task Force on Preventative Health Care
WES (2013) (423)	[1] Diagnosis [2] Infertility management	[1] Healthcare professionals (unclear) [2] Women with endometriosis (unclear)	Unclear	Database: not reported Search terms: not reported Language: English Dates: 1985 - 2010	Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

	[3] Pain management	[3] Pharmaceutical employees (unclear) [4] Researchers (n=56; International; 17 countries)		Detailed search strategy: not reported Inclusion / exclusion criteria: not reported	

Abbreviations: ACCEPT: Australasian CREI Consensus Expert Panel on Trial Evidence (2012); ACOG: The American Congress of Obstetricians and Gynecologists (2010); CENTRAL; CNGOF: Collège National des Gynécologues et Obstétriciens Français (2006); ESHRE: ESHRE (2014); NGG: National German Guideline: Guideline for the Diagnosis and Treatment of Endometriosis (2014); SD: Standard deviation; SOGC: The Society of Obstetricians and Gynaecologists of Canada (2010); WES: World Endometriosis Society (2013).

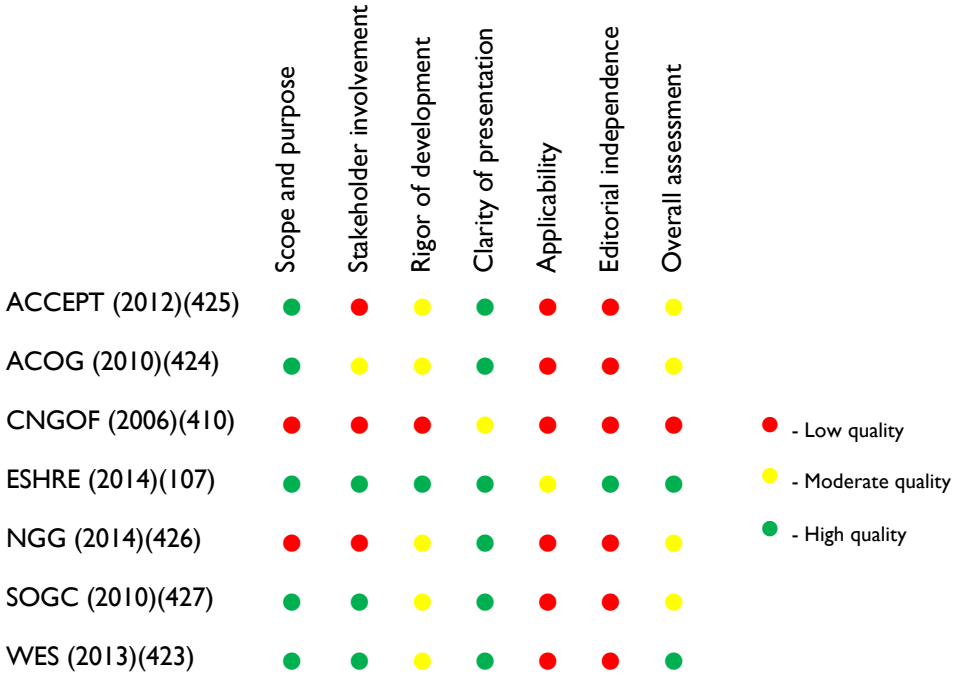
Assessment of methodological quality

A systematic review was described by the majority of guidelines (107,423–427), however, no guideline explicitly described the all six methodological features (table 15). The most commonly reported feature, naming of the database(s) searched, was described by five (73%) guidelines (107,424–427).The most detailed guidelines reported three features (50%) (424,425,427), while the CNGOF (410) guideline reported no features. There was no guideline which reported a detailed search strategy or described an inclusion or exclusion criteria for the evidence they sought.

Four guidelines did not report a consensus method (410,424,426,427). The majority of guidelines (107,423,425–427) reported the inclusion of multiple stakeholder groups, however only three guidelines (107,423,426) clearly report the inclusion of women with endometriosis in its development. Quality assessment of retrieved references was described by five guidelines (107,423–425,427). Assessment methods included: [1] Grading of Recommendations Assessment, Development, and Evaluation (107,423); [2] Canadian Task Force on Preventative Health Care (427); [3] National Health and Medical Research Council (425); and [4] United States Preventative Services Task Force (424).

Two guidelines were assessed as high quality (107,423), four guidelines were assessed as moderate quality (424–427) and one guideline was assessed as low quality (Table 16) (410). Guidelines were typically of high quality in the domains of clarity and presentation and scope and purpose. Guidelines were of moderate quality in the domains of stakeholder involvement and rigor of development. Guidelines were of low quality in the domains of applicability and editorial independence (Table 16).

Table 16 - *Methodological quality of endometriosis guidelines.*



Recommendations for clinical practice

We extracted all statements recommending clinical practice in the domains of [1] diagnosis (36 recommendations); [2] medical management for pain (30 recommendations); [3] surgical management for pain (39 recommendations); [4] Artificial reproductive techniques for infertility (12 recommendations); [5] surgical management of infertility (22 recommendations); and [6] alternative treatments for pain and infertility (13 recommendations). A total 152 separate recommendations were included for analysis. Only ten (7%) of 152 recommendations were comparable and cited by all guidelines (Table 17 and Table 18) (Appendices 3-5). The comparable recommendations are underlined in appendices 3-5. We summarised the variation in recommendations of all medical treatments for pain associated with endometriosis described across all included guidelines (Table 19).

Table 17 - *Guideline recommendations for the diagnosis of endometriosis.*

	Mild / moderate endometriosis					Severe endometriosis					Endometrioma				
Guideline	Symptoms	Examination	Imaging	Biochemical	Surgical	Symptoms	Examination	Imaging	Biochemical	Surgical	Symptoms	Examination	Imaging	Biochemical	Surgical
ACOG (2010)(424)	•			•	•	•		•					•		
CNGOF (2006)(410)		•	•	•	•		•	•				•	•		
ESHRE (2014)(107)	•	•		•	•		•	•		•		•	•		•
NGG (2014)(426)			•	•	•		•	•				•	•	•	•
SOCG (2010)(427)	•	•	•	•	•	•	•	•	•			•	•	•	•

• Recommendations

World Endometriosis Society (2013) (423) and Australasian CREI Consensus Expert Panel on Trial Evidence (2012) (425) provide no recommendations for the diagnosis of endometriosis.

Table 18 - *Level of evidence supporting recommendations.*

Example 1: Biomarkers should not be used to diagnose endometriosis.

Level of Evidence / Guideline	Cochrane review	Systematic review	Randomised trial	Non randomised trial	Expert opinion	No reference
ACOG (2010)(424)				•		
CNGOF (2006)(410)						•
ESHRE (2014)(107)		•				
NGG (2014)(426)		•				
SOCG (2010)(427)		•				

• Recommendation stated

Example 2: Diagnostic laparoscopy and histopathology should be used to diagnose endometriosis.

Level of Evidence / Guideline	Cochrane review	Systematic review	Randomised trial	Non randomised trial	Expert opinion	No reference
ACOG (2010)(424)						•
CNGOF (2006)(410)						•
ESHRE (2014)(107)					•	
NGG (2014)(426)		•	•	•		
SOCG (2010)(427)						•

• Recommendation stated

* World Endometriosis Society (2013)(423) and Australasian CREI Consensus Expert Panel on Trial Evidence (2012)(425) provide no recommendations for the diagnosis of endometriosis.

Table 19 - *Medical intervention for pain associated with endometriosis.*

Recommendation (number of guidelines) / **Intervention**	Use	Use in some circumstances	Do not use	Absent	Ambiguous
Hormonal					
Aromatase Inhibitors		2		4	1
Combined oral contraceptive pill	6			1	
Gonadotropin releasing hormone analogue	3	3		1	
Levonorgestrel-releasing IUS	4			2	1
Progestagens	6			1	
Selective progesterone receptor modulator	1	4		2	
Non-hormonal					
Anti-tumour necrosis factor alpha			1	6	
Chinese medicine				6	1
Fish oil		1		6	
Lactic ferments				6	
Magnesium	1			6	
Minerals		1		6	
Pentoxifylline			1	6	
Rosiglitizone				6	1
Salts		1		6	
Valproic acid				6	1
Vitamin B1 & B6	1			6	
Other					
Acupuncture	1			6	
Physiotherapy			1	6	
Psychological	1			5	1
Transcutaneous electrical nerve stimulator	1			6	

Five guidelines report recommendations for the diagnosis of endometriosis. Recommendations for diagnosis of endometriosis totalled 36 (Table 17) (Appendix 3). Seventeen recommendations (47%) citied no research evidence or expert opinion. Four recommendations were described by all five guidelines (107,410,424,426,427). These recommendations were: [1] histological confirmation is recommended for the diagnosis of mild to moderate endometriosis (Table 18); [2] biomarkers are not recommended for

the diagnosis of endometriosis (Table 18); [3] histology is recommended to confirm diagnosis; and [4] transvaginal ultrasound imaging is recommended for the diagnosis of endometrioma (Appendix 3).

Recommendations for the medical management of endometriosis associated pain totalled 30. Three recommendations (10%) citied no research evidence or expert opinion. Three recommendations were described by all guidelines (107,410,423,424,426,427). These recommendations were: [1] the COCP is recommended for endometriosis associated pain; [2] progestogens are recommended for endometriosis associated pain; and [3] gonadotropin releasing hormone analogues are recommended for endometriosis associated pain (Appendix 4). We summarised the variation in strength of recommendations highlighting the variation in clinical advice between international and national guidelines (Table 19).

Recommendations for the surgical management of endometriosis associated infertility totalled 21, four (19%) of these cited no research evidence or expert opinion (Appendix 5). A single recommendation, surgery improves fertility with endometriosis associated subfertility, was described by all guidelines (107,410,423–427). Alternative interventions to manage endometriosis associated pain was infrequently discussed and the benefits of psychological therapy was seldom reviewed (Appendix 5).

Additional comparable recommendations across all guidelines include: laparoscopic uterosacral nerve ablation (LUNA) does not improve endometriosis associated pain; and Gonadotrophin releasing hormone analogues (GnRHa) can be used as an adjunct prior to IVF (Appendix 4-5).

Research evidence supporting recommendations

The number of references cited in each guideline ranges from 0 (410) to 211(426) with publication years between 1925 through 2014 (Appendix 3-5). The total number of Cochrane systematic reviews used within each guideline ranged from 0 (410) – 25 (423)

and the number of RCTs used ranged from 0 (410) – 28 (427). Where available we sought the original references used to generate recommendations. We summarised the references and study design type used to form each individual guideline (Appendix 3-5).

7.5 DISCUSSION

Main Findings

There is significant variation in endometriosis guidelines. No guideline followed the standardised approach to guideline development advocated by AGREE-II guidelines. The involvement of women with endometriosis varied significantly. The consensus method for recommendation development was clearly described in only two guidelines. No guideline addressed endometriosis care in a low-resource setting. The funding-sources and conflicts of interest were poorly described with competing interests frequently not reported. These findings justify the critical appraisal of these guidelines, especially in an area such as endometriosis management, where diagnosis and treatment strategies are deemed suboptimal (428). A total of 152 separate recommendations exist across seven guidelines, only ten recommendations (7%) are comparable across guidelines. With differences in guideline development methods it is not surprising to find there was a paucity of comparable recommendations with wide intra-guideline variation in the supporting evidence.

Strengths and Limitations

The strengths of this systematic review includes its originality, robust search strategy, and methodological design. To our knowledge, this is the first study to systematically appraise the methodological quality and map the recommendations of endometriosis guidelines. There was good agreement between all four reviewers with discrepancies resolved quickly through discussion. We involved a patient representative (C.B.) in the design and conduct of our research.

Systematic reviews are not without limitations. Several studies have highlighted limitations of the AGREE-II instrument (422). The subjectivity of scoring the domain items, and the overall score has not been definitively associated with implementation. However, it is important to note the association between domain score for applicability

and the guidelines' use in clinical practice (429). We did not calculate weighted kappa to explore agreement between authors as the statistical level of agreement required in health research is unclear and it is not currently recommended by the Cochrane Collaboration (395,405). We could have considered systematically reviewing the RCTs and systematic reviews to form a judgement on the appropriateness of guideline recommendations. However, this would be unlikely to yield substantial benefit in the context of the considerable resource allocation required.

Interpretation

Guidelines are developed by searching, collecting, and collating evidence to make value judgements through consensus. The methods to achieve this in an unbiased manner are described clearly in the Appraisal of Guidelines for Research and Evaluation in Europe (AGREE-II) criteria. A recent Institute of Medicine report on guideline development and their worth in modern clinical practice highlights widespread methodological limitations in formation (430). This review highlights the shortcomings in methodological areas of stakeholder involvement, rigor of development, applicability and editorial independence of guidelines for the diagnosis and management of endometriosis.

Guideline developers can be prohibited by the availability of research evidence to answer the questions raised. It is well known that research in the area of obstetrics and gynaecology, as in other fields, is lacking RCT evidence (431). There is wide outcome reporting variation within those few RCTs making synthesis into systematic review or guideline recommendations difficult (384). The selection of predefined appropriate outcomes within endometriosis research is essential to reduce bias and enhance guideline formation. The development and use of a collection of well-defined, discriminatory, and feasible outcomes termed a core outcome set would help to address the concerns of data deficiency which prohibit guideline formation. Core outcome sets represent a minimum number of outcomes chosen by the key stakeholders and do not confine a particular trial or systematic review to the core outcome set.

A poor search strategy will exacerbate the difficulties of highlighting research to answer clinical questions. This can result in difficulties making clear recommendations in the absence of high quality evidence. In this systematic review, the description of specific search terms was only reported in a single guideline (425). No guideline published a detailed search strategy.

A total of 42 (28%) of the 152 recommendations had little or no scientific background. These were either unreferenced or supported by expert opinion (Appendices 3-5), which are particularly susceptible to bias (431). It is important to consider the number of guidelines, which considered a particular modality of diagnosis or treatment in the interpretation of the reliability and strength of agreement. There was considerable variation in the references used to inform identical recommendations between guidelines. This represents significant methodological variation in study selection, study assessment, or data interpretation between individual guidelines development groups.

These findings remain consistent with a previous study (421) reporting the low quality of guidelines for pain associated with endometriosis. Limited progress has been demonstrated in the development of guidelines for the diagnosis and management of endometriosis in over a decade. The development of guidelines without a standardised methodological process will lead to the omission of beneficial therapies, preventable harm, and suboptimal patient outcomes or experiences. This review has demonstrated that even highly trusted guidelines suffer from limitations in their development process. Most guidelines were of low quality for the domain ‘applicability’. This domain obtained remarkably low scores, as most guidelines did even not discuss the topics of practical implementation, barriers to application, costs and monitoring/auditing criteria. These findings are of concern given the intensity and cost of efforts to generate an ever-increasing body of guidelines that are not used (432). In future guidelines, more attention has to be paid to providing advice on how the recommendations should be put into practice.

As a whole, guidelines were of moderate quality for the domain of stakeholder involvement. Three (107,423,426) of the seven guidelines involved patients in the development of their guideline. This finding illustrates the minimal patient participation in the guidelines creation and the little importance placed on their involvement. Endometriosis is a chronic disease which can result in long term symptoms for sufferers. Chronic diseases require greater patient representation in guideline development as there may be a perceived mismatch between clinician and patient priorities. The multidisciplinary contribution serves to broaden the approach to health care problems, increase completeness of evidence finding strategies and help to identify hurdles to implementation.

The development of guidelines is an expensive and time consuming process. Currently there are seven international and national organisations who develop guidelines. Despite an electronically connected academic society with a single pool of research evidence to guide, there remains multiple suboptimal guidelines for the diagnosis and management of endometriosis. There are no universally agreed recommendations for the diagnosis and management of endometriosis associated pain and subfertility. A coordinated approach toward developing updated, evidence-based, international, expert consensus recommendations for the diagnosis and management of endometriosis is needed. A single guideline which follows the AGREE-II guidelines for development will reduce variation in clinical care and prevent patient harm.

There is a strong coordinated move toward higher-quality published research, initiated by CoRe Outcomes in Womens's and Newborn health (CROWN) Initiative, and supported by journal editors including the *Journal of Obstetrics and Gynecology* (433). These highly influential journals editors will, where present, encourage the publication of studies using outcomes from a core outcome set. The implementation of core outcome sets will augment the production of comparable data for improved evidence-synthesis within clinical guidelines (382,434). This will improve the delivery of evidence based patient

care. International and national stakeholders including the World Health Organisation, the National Institutes of Health, and the Cochrane Collaboration are committed to supporting, developing, and implementing core outcome sets across women's health.

7.6 CONCLUSION

Despite highlighted methodological deficiencies over a decade ago, there remains substantial variation in quality and content within international and national guidelines for the diagnosis and management of endometriosis. This could lead to unjustified and unwarranted variations in patient care. This variation in care could lead to some patients benefiting from improved outcomes however, many patients will suffer harm as a result. There is evident need for more consistent synthesis of evidence for guideline formation. This would be facilitated by the implementation of a core outcome set within future endometriosis trials, systematic reviews and clinical guidelines.

This chapter is based on the following peer reviewed publication:

Hirsch, M., Begum, M. R., Paniz, É., Barker, C., Davis, C. J. and Duffy, J. M. N. Diagnosis and management of endometriosis: a systematic review of international and national guidelines. BJOG: Int J Obstet Gy. doi:10.1111/1471-0528.14838

CHAPTER 7:

INVESTIGATING THE ROLE OF SURGERY IN THE TREATMENT OF OVARIAN ENDOMETRIOSIS IN WOMEN WITH SUBFERTILITY

In this chapter I explore the role of surgical therapies for the management of ovarian endometrioma in the context of subfertility.

8.1 BACKGROUND

Background: The optimal surgical management technique of ovarian endometrioma amongst women with endometriosis associated subfertility is not known. Recent studies demonstrate an adverse effect of some techniques on surrogate markers of ovarian reserve amongst women with ovarian endometriosis. Convincing evidence of a benefit of surgery on fertility outcomes is lacking.

Objective: To review the current surgical management of ovarian endometriosis amongst women with subfertility and summarise the results.

8.2 BACKGROUND

Endometriosis affects up to 10% of women of reproductive age yet its aetiology is poorly understood. The disease has three common manifestations; ovarian endometriosis, peritoneal endometriosis and DIE (90). Ovarian endometriosis can manifest as deposits on outside of the ovarian cortex or as Ovarian endometriomata (OE). The theories behind formation of OE include Sampson et al (59) who hypothesised that refluxed endometrial deposits on the ovarian cortex cause adhesions to the uterus causing a cavity which expands forming an OE. To contrast this, Brosens et al (435) speculate that OE are formed from the invagination of superficial ectopic endometrial deposits on the ovarian cortex. A further and more recent theory from Vercellini et al (436) suggests that refluxed endometrial deposits lead to ovarian adhesions with the pelvic peritoneum. This area of adhesion progresses on to the invagination of the external ovarian cortex leading to the formation of a pseudocyst. Regardless of aetiology, OE are common, found in 17-44% of women with endometriosis, (437) of which between 2-50% can be asymptomatic (98).

The clinical manifestation of OE is often pelvic pain and or subfertility (438). The mechanisms responsible for increased rates of subfertility are unclear yet theories of endometriosis-mediated subfertility include: 1) impaired tubal function as a result of adhesions from pelvic endometriosis 2) adverse effect on ovulation; 3) reduced oocyte quality; 4) reduced ovarian reserve mediated through pressure atrophy; 5) reduced vascularisation of normal ovarian cortex from expanding OE, and/or through an inflammatory reaction to OE (439). Theories of clinical symptoms are discussed in section 1.4.

Treatments for OE or symptoms secondary to OE include expectant management, medical management, and surgical management. Medical treatments are commonly successful at reducing the size of the OE but only during treatment, after which they

return to their original size. Surgical treatments aim to destroy or remove the OE (171(240).

Surgical treatment of OE can also have an adverse effect on ovarian reserve (440,441). This has led to debate over the optimal surgical technique for the treatment of OEs. There has been a shift of opinion over the past decade with clinicians favouring a more conservative approach in the management of OE. This is particularly amongst women with subfertility. In this review, we will examine the recent data on the different surgical techniques for managing endometrioma in a fertility clinic setting.

8.2.1 THE SHIFT OF OPINION

A 2010 survey of European Gynaecologists suggested that surgery was the most common management strategy for OE (442). This was based on international guidelines (ESHRE 2005) suggesting that endometriomas >4cm in diameter should be treated surgically. This was believed to improve fertility in the following domains: 1) increased spontaneous pregnancy rates; 2) facilitate access to the ovaries during transvaginal oocyte retrieval (TVOR); 3) reduce the risk of infection at TVOR; 4) provide a histological diagnosis; and 5) improve response to controlled ovarian hyperstimulation (COH) (104). Laparoscopic ovarian cystectomy with stripping the cyst wall from the ovarian cortex was the preferred route and surgical technique. This has favourable improvements in fertility and pain symptoms together with lower recurrence rates when compared to drainage and electrocoagulation (238).

The potential adverse effects of surgical interventions for OE prior to ART include reduced ovarian reserve (443). A recent Cochrane review (240), showed no evidence of benefit on clinical pregnancy rates from surgery for OE compared to expectant management. This review highlighted concerns that cystectomy appeared to reduce ovarian response during COH with no effect on the number of oocytes retrieved. The

review was unable to report live birth as this outcome was not reported by a single trial. Since this robust review, several further trials have expressed concerns of the potential adverse effect of surgery for OE, highlighting the lack of convincing evidence for improved pregnancy outcomes in women with OE surgery followed by ART (76,444–446).

The concerns of harm without convincing evidence of benefit has led to a recent change of clinical recommendations from both the American Society for Reproductive Medicine and ESHRE supporting conservative management of OE prior to ART treatment (107,447). The 2013 ESHRE guidelines clearly describe the indications for surgery: 1) OE >3cm in diameter; 2) pain symptoms; and 3) improve access to ovarian follicles during ART. Importantly, women undergoing surgery should be counselled about the risk of reduced ovarian reserve and the potential loss of the ovary (107).

8.3 ENDOMETRIOMA AND OVARIAN RESERVE: INHERENT OR IATROGENIC INJURY?

The effect of OE on ovarian reserve has been the subject of much controversy in recent years. Ovarian reserve is measured using markers including: 1) ultrasonic markers such as antral follicle count (AFC); 2) biochemical markers including anti-Müllerian hormone (AMH) and follicle stimulating hormone (FSH) levels; 3) histological markers such as follicular density and perhaps most importantly; and 4) clinical markers including response to COH and pregnancy rates. There is no single marker to determine function or capacity of the ovary at any given stage, therefore, these are referred to as surrogate markers of ovarian reserve.

The mere presence of OE has been associated with a reduced ovarian reserve as evidenced by a 31% reduction in ovulation rate in ovaries containing OEs compared to

healthy ovaries (75) and lower baseline AMH levels in the presence of OEs (448,449). Clinical surrogate markers of ovarian reserve have also suggested an adverse effect of the presence of OE on COH (450). Histological studies have also suggested that OEs have an adverse effect on ovarian reserve as evidenced by reduced follicular density in ovarian cortex surrounding OEs compared to cortex around other benign cysts (451–453), especially in younger patients (<35 years old) (454). However, there has been no reduction in ovarian response to COH when comparing ovaries containing small (<3cm) endometriomas to unaffected ovaries (455–457) suggesting that the size of OE is important in determining the effect on ovarian response. It has been shown that small (mean diameter 23mm) bilateral OEs have a combined effect on ovarian response as evidenced by a reduced number of developing follicles during COH. However, there is no demonstrable effect on oocyte quality or clinical pregnancy rates (458).

Mechanisms of surgical damage include accidental removal of healthy tissue during endometrioma cystectomy and direct damage to ovarian cortex following surgical haemostasis and scar tissue formation.

Earlier reports had shown a reduced ovulation rate following endometrioma surgery (75,459) but more recent research has focused on the effect of surgery on surrogate serum markers of which AMH has been shown to be the most reliable (460,461). Two recent meta-analyses (440,441) showed strong evidence of sustained reduction in post-operative AMH levels of up to 40% after ovarian surgery, with the decline being more pronounced in bilateral surgery and in women over 38 years old (462). Further studies have shown a sustained reduction in AMH levels for at least 6 months after surgery (462–465). This correlates with the bilaterality and severity of endometriosis (466) and with cyst size (467). Interestingly, two groups have demonstrated a partial recovery in AMH levels up to 65% of pre-operative levels three months after surgery (468,469).

Mechanisms implicated in this recovery of ovarian function include re-vascularisation after surgery, compensation from remaining follicles or an unaffected ovary (439) and rearrangement of follicle cohorts (470).

Histological studies offer an explanation for this partial recovery with healthy ovarian tissue removed in 85-97% of excised endometrioma specimens (454,471,472). The size of the endometrioma is an important determinant of the amount of healthy tissue removed, with 200μm of tissue lost per cm increase in cyst diameter (471). Healthy ovarian tissue is found in the majority of endometrioma cyst wall specimens, even in the hands of experienced surgeons (473). There is little evidence to suggest that the degree of surgical experience, among appropriately trained laparoscopic surgeons, has a significant detrimental effect on post-operative ovarian reserve (474–476).

8.4 TREATMENT OPTIONS FOR OE

8.4.1 SURGICAL THERAPIES

The intended advantages of surgery for OEs include: obtaining a histological diagnosis of the cyst (0.8% risk of occult malignancy (477)); improving clinical symptoms; improving monitoring of follicular growth; access to the follicles during ART; and reducing the small risk of spontaneous endometrioma rupture (478–480).

Disadvantages of surgery include; adverse effect on ovarian reserve, delay in commencing ART, the cost of surgery (481) and the risk of surgical complications (482).

Successful surgery is a balance of removing the maximum amount of endometriotic tissue, reducing the risk of recurrence, whilst keeping bleeding at a minimum, and minimising the need for haemostatic measures that can damage the ovarian reserve.

Surgical techniques that have been described in the literature include laparoscopic drainage and ablation (with various different energy sources), laparoscopic cystectomy (using the stripping technique), combination techniques, the vasopressin technique

(aiming for relatively bloodless hydrodissection with diluted vasopressin) and aggressive treatment in the form of oophorectomy. In centres in which minimal access surgical expertise is not available, open surgery still has a role (483).

Comparing the two commonest techniques of ovarian cystectomy vs drainage and ablation through a recent systematic review showed that laparoscopic cystectomy has lower recurrence and higher spontaneous pregnancy rates (484).

Plasma energy coagulation is an alternative energy modality which offers a low depth of tissue penetration (<1.5 mm), limiting damage to the healthy ovarian tissue (485). Preliminary studies demonstrate small beneficial effect on markers of ovarian reserve compared with ovarian cystectomy (486) with comparable recurrence and pregnancy rates (487). The clinical relevance of these results remains to be confirmed in a large RCT.

Recent evidence has suggested that using alternative methods to achieve ovarian haemostasis rather than bipolar diathermy has a beneficial effect on markers of ovarian reserve. Methods include haemostatic sealants along with ovarian suturing to achieve haemostasis following cystectomy (488,489). Despite risks of suturing induced ischaemic changes and postoperative adhesions that can adversely affect ovarian function suturing is believed to be favourable in the context of subfertility.

Combined techniques have also shown promising results. Partial cystectomy of 80 – 90% of the endometrioma wall combined with CO_2 laser vaporisation to the ovarian hilum (in which the plane of cleavage is not easily identified) maintained postoperative ovarian volume and AFC, and resulted in a low recurrence rate (2%) and a 41% spontaneous pregnancy rate at a mean follow-up of 8.3 months (490). A three-step technique of laparoscopic cyst drainage, treatment with GnRHa for three months before a repeat laparoscopic laser ablation of the cyst wall, resulted in improved AFC and AMH at follow up when compared with routine ovarian cystectomy in a small RCT (491).

Finally, two recent studies (492,493) have shown promising results using the vasopressin technique, in which a solution of diluted vasopressin was injected in the endometrioma cyst wall prior to cystectomy. Employing this technique, the hydro-dissection can help identify the plane of cleavage, whilst the vasoconstrictive effect of vasopressin reduces the need to use other haemostasis control methods and thus helps preserve ovarian function.

Surgery with combined Medical therapy

A single study assessing 125 patients evaluated the impact of surgery with a combined medical therapy for the treatment of OE. The medical therapies assessed were GnRH-a, 3.6mg every month for 3 months.

This study performed a prospective comparative analysis of a cohort of participants with stage II-IV endometriosis and OE noted on ultrasound. The cohort all underwent conservative laparoscopic ovarian cystectomies with half the group being subsequently allocated to hormonal therapy and half to no post-operative medical therapy. There was a significant increase in spontaneous pregnancy rate (57.1% vs 36.8%) amongst those taking GnRH-a within the 18 month follow up period along with a significant reduction in cyst recurrence seen in the experimental group (12.7% vs 27.4%).

There was a significant rise in post-operative FSH at 3 months compared to pre-operative levels amongst the control group. This was not seen in the experimental group and may be due to pituitary suppression induced by the GnRH-a.

Ultrasound guided drainage & Sclerotherapy

The concerns regarding the effect of surgery on ovarian function together with the surgical risks associated with a surgical approach to treating OE have led researchers to seek less invasive treatments such as ultrasound scan (USS) guided drainage, usually combined, with irrigation with a sclerosing agent. Sclerosing agents tried in the past include ethanol (497)], tetracycline (498), synthetic IL-2 (499) and methotrexate (500). Results have demonstrated conflicting evidence with recurrence rates varying between 5.4% - 83.3% at follow up of less than a year (501). Concerns surround the risk of abscess formation and missing occult malignancy, and lack of improvement in reproductive outcomes after ART (502–505). No major complications have been

reported in patients, but a recent study on an animal model of albino rats, endometrioma aspiration and ethanol sclerotherapy raised the concern of a reduction in the ovarian reserve following the treatment (506).

Overall, USS-guided endometrioma drainage does not seem to have a role in the current management of the disease as it has a poor efficacy in relieving the symptoms and a high risk of introducing infection and cyst recurrence (507). It may, however, have a role in facilitating oocyte retrieval in patients who decline or are not fit for surgery to improve access to follicles.

8.8 CONCLUSIONS

Ovarian endometriosis remains a challenging disease. There is growing evidence that both the physical presence of OEs and the surgery to remove them can further adversely affect ovarian function and thus the consensus has now shifted towards a more conservative approach in treatment (107,423,447).

The positive effect of ovarian cystectomy on spontaneous pregnancy rates has wrongly been extrapolated as a positive effect on assisted reproduction technology (ART) outcomes leading to the widely accepted practice of surgical treatment for OE prior to embarking on ART treatment such as in-vitro fertilisation (IVF) or intra-cytoplasmic sperm injection (ICSI). A meta-analysis in 2009 found no adverse effect of surgical treatment of endometriomas on the outcomes of ART treatment when compared to conservative management (239). Surgery can severely compromise ovarian reserve with

premature ovarian failure reported in up to 16.3% (508) and a 13% rate of failure to respond to gonadotrophin stimulation (445) have been reported.

There is marked heterogeneity in disease and surgical technique among the reported studies with a relative paucity of evidence from high quality RCTs(240). Determining the optimal surgical technique requires a greater volume of comparable high quality evidence. This was conformed in a recent Cochrane systematic review of interventions for the management of endometrioma prior to ART found no studies reporting live birth as a primary outcome. This highlights the difficulties of outcome reporting variation that was discussed in chapter 4. These significant methodological difficulties are likely to result in delays establishing the optimal surgical technique.

A more rounded view on the clinical scenario including: severity of symptoms; concern regarding malignancy; access to follicles; and desire to preserve fertility should be taken into consideration prior to performing surgery for OEs. The decisions need to be on a case-by-case basis after fully informed consent, including a 2.4% risk of immediate ovarian failure following bilateral ovarian cystectomy (509). We recommend that surgery should be reserved for symptomatic patients after their family is complete. Repeat surgery is best reserved until fertility is no longer desired however, with delayed conception, this is becoming a more frequent challenge.

For patients with subfertility and OEs the ovarian reserve and other fertility parameters should be assessed pre-operatively with subsequent triage for ART treatment or surgery depending on age and ovarian reserve. ART should be considered as the first option

where there is evidence of reduced ovarian reserve. This should also be the case for patients with small (<3cm) OEs as these do not appear to affect the outcome of ART.

The focus of research has been heavily targeting the easily collected and easily reported surrogate markers of fertility such as AFC, AMH, and FSH without reporting live birth, arguably the primary reason that a patient attends the fertility clinic.

The key to successful surgery may be to avoid the need for diathermy induced haemostasis, as this has been shown to compromise ovarian function(510). Surgical skill is required to perform the optimal balance minimising ovarian damage against complete cyst excision. Whatever the skill level, it is essential that the patient be aware of the benefits and risks involved, reaching an individualised treatment plan avoiding permanent irreversible ovarian damage. Overall, there is growing consensus that OEs should not be routinely removed prior to ART. Research should be focused on improving the surgical techniques which best preserve post-operative ovarian function, for those individual patients where an operation is deemed necessary. A harmonised approach to reporting key outcomes important to patients, clinicians and researchers needs to be developed to maximise the usefulness of future research to improve patient care.

This chapter has been adapted and updated from the following peer reviewed publication:

Psaroudakis D, Hirsch M, Davis C. Review of the management of ovarian endometriosis: paradigm shift towards conservative approaches. Curr Opin Obstet Gynecol. 2014 Aug;26(4):266-74.

CHAPTER 8:

THE LONG TERM RISKS OF HYSTERECTOMY AND BILATERAL OOPHORECTOMY FOR WOMEN WITH ENDOMETRIOSIS – A SYSTEMATIC REVIEW AND META-ANALYSIS

9.1 ABSTRACT

Background:

There are over 2,000 hysterectomies performed each day in the United States of America, frequently with bilateral oophorectomy. We performed a systematic review and meta-analysis, investigating if health outcomes are altered by adding bilateral oophorectomy to hysterectomy for benign indications.

Methods:

We searched CENTRAL, Embase, and MEDLINE from their inception to August, 2015. We included observational studies that followed up women undergoing hysterectomy, with or without bilateral oophorectomy, for a range of health outcomes. We used the Newcastle-Ottawa Scale to assess the methodological quality. We computed, using random effects meta-analysis, risk ratios (RR) for various outcomes comparing women with *vs* without bilateral oophorectomy.

Findings:

Of 13,470 citations, there were 48 relevant studies (1,272,071 women). Hysterectomy with bilateral oophorectomy (498,603 women) *vs* without (773,468 women) was associated with increase in stroke (RR 1.09, 95% CI 1.03 – 1.16; baseline risk = 35%; number needed to harm [NNH] = 32) and anxiety (RR 1.26, 95% CI 1.06 – 1.51; baseline risk =5.9%; NNH = 65); and decrease in ovarian cancer (RR 0.09, 95% CI 0.04 – 0.19; baseline risk = 2.5%; number needed to treat [NNT] = 44); and breast cancer (hazard ratio 0.85, 95% CI 0.73 – 0.99; baseline risk = 12%; NNT = 55).

Interpretation:

The balance of adverse and beneficial health outcomes associated with bilateral oophorectomy should be employed when counselling women concerning benign hysterectomy.

9.2 INTRODUCTION

Hysterectomy for benign disease such as leiomyoma, abnormal uterine bleeding, endometriosis, and pelvic pain is the most common gynaecological operation with over 2,000 procedures performed daily in The United States of America (511). Women face a choice at operation as to whether their ovaries are conserved or removed. Ovarian hormone production provides health benefits both before the menopause and extending into later life (512,513). An oophorectomy leads to a fall in circulating oestrogen and androgen levels which may have clinically significant consequences on mortality, bone health, malignancy, cardiac risk, and mental health (514).

There are no national or internationals recommendations for the pre-menopausal conservation or removal of ovaries in women with benign gynaecological disease (424). The routine inclusion of bilateral oophorectomy is common clinical practice occurring in up to 30% of all hysterectomies under age fifty (515) and increasing in frequency (516). The commonest indication cited is the reduction in the lifetime risk of developing ovarian cancer (424) which remains low at 1.4% (517). Reviews of comparisons for long term health outcomes between women having undergone hysterectomy with and without bilateral oophorectomy are limited. We lack evidence syntheses to guide future clinical practice and individual decision making in decisions surrounding ovarian conservation at the time of hysterectomy (518).

We conducted a systematic review and meta-analysis to investigate the association between hysterectomy with or without bilateral oophorectomy, and various health outcomes.

9.3 METHODS

A protocol with explicitly defined objectives, criteria for study selection, approaches to assessing study quality, and statistical methods was developed and prospectively registered with the International PROSPERO (registration number CRD42015026411). We reported the systematic review and meta-analysis in accordance with PRISMA (328).

SEARCH STRATEGY AND SELECTION CRITERIA

We performed a comprehensive and systematic search of the following databases from their inception to August, 2015: CENTRAL, January 1, 1898 – August 21, 2015), Cochrane Database of Systematic Reviews (CDSR), Cochrane Groups, Cochrane Library, Cochrane Methodology Register (CMR), Database of Abstracts of Reviews of Effects (DARE), Economic evaluations, Embase (January 1, 1947 – August 21, 2015), Health technology Assessment Database (HTA), Medline (January 1, 1946 – August 21, 2015). We performed keyword and MeSH searches for “hysterectomy” and checked reference lists of relevant papers and reviews for additional studies. The search was limited to studies on humans but was not limited by language.

Two independent reviewers (MH & JOK) worked in duplicate to screen the titles and abstracts in Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia) (519) for eligibility. We retrieved all relevant citations and reviewed the full texts. Any disagreements were resolved through discussion with a senior investigator (JD & KK). We excluded conference abstracts, case reports, and case series.

The predefined inclusion criteria were, observational studies, including cohort and case-control designs, in any language with adult female patients undergoing hysterectomy were included. We compared hysterectomy with bilateral oophorectomy to hysterectomy with ovarian conservation. We excluded studies where hysterectomy was undertaken for malignant disease.

Outcomes studied were: [1] all-cause mortality; [2] cardiovascular disease; [3] coronary heart disease; [4] stroke; [5] malignancy; [6] osteoporosis; [7] neurological disease; [8] depression; and [9] anxiety. We measured outcomes from 5 years postoperatively for cardiovascular disease, coronary heart disease, and stroke. We measured outcomes from 1 year for malignancy, osteoporosis, neurological disease, depression and anxiety. We investigated whether study participants were users of hormone replacement therapy (HRT). Any factors statistically corrected for in the data we extracted and recorded.

DATA EXTRACTION AND QUALITY ASSESSMENT

Two independent investigators (MH & JOK) extracted data using a standardised, pre-designed data extraction in Microsoft Excel 2013. If data were presented following multivariable adjustment they were selected over non-adjusted data. Disagreements were resolved by discussion with a senior author (JD & KK). We contacted authors where data was not presented within the manuscript (520–525).

We assessed methodological quality and risk of bias of the included studies with criteria set by the Newcastle-Ottawa Scale (526). Two reviewers (MH & JOK) undertook quality assessment independently and in duplicated according to the pre-defined criteria. A low risk of bias was attributed to studies that scored four stars for selection, two stars for comparability, and three stars for ascertainment of the outcome. Medium risk of bias allocated to studies with two or three stars for selection, one for comparability, and two for outcome ascertainment. All studies with a score of one for selection or outcome ascertainment, or zero for any of the three domains, was regarded as having a high risk of bias (527).

DATA SYNTHESIS

We tabulated characteristics and results of all included studies. We compared health outcomes in women undergoing hysterectomy with oophorectomy to women undergoing

hysterectomy alone. After pooling data we reported the random and fixed effects meta-analysis as RR with 95% CIs. Heterogeneity was assessed as I^2 statistic. We calculated number need to treat (NNT) and number need to harm (NNH) for all statistically significant outcomes. We used the following formula: NNT/NNH = 1/baseline risk x (1-RR). The baseline risk was calculated from the control group of the highest quality study which reported the specified outcome. We attempted to perform subgroup analysis by age, HRT use, and menopausal status however this data was not available from the included studies.

ROLE OF THE FUNDING SOURCE

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

9.4 RESULTS

Searches of electronic databases and reference lists generated 13,470 references. On evaluation of their titles and abstracts, 338 articles (2.5%) were potentially relevant for detailed assessment (figure 19), and of these 48 studies (517,520–522,524,525,528–569), comprising 1,272,071 women, met our inclusion criteria for quantitative synthesis (Table 20). We included 24 studies (517,520,528–535,537,541–543,554,556,559–561,563–565,567,569), comprising 760,186 women for meta-analysis (Table 20). Of the 48 studies, 24 were cohort, 11 case-control and 13 cross-sectional. There were 41 different population-based cohorts (517,520–522,524,525,528–569). These included data from the following study populations: Black Women's Health Study (535); Breast Cancer Detection Demonstration Project (536); Cancer prevention study II (543); DOM Project (534); Early postmenopausal Interventional Cohort study (520); Eindhoven Perimenopausal Osteoporosis Study (525); Framingham Study (567); Kuopio Osteoporosis Risk Factor and Prevention Study (522); Maryland Women's Health Study (564); Mini-Finland Health Survey (529,546); National Climacteric Survey of the Mexican Association for the Study of the Climacteric (563); Nurses' Health Study (531–533,566); Rancho Bernardo Heart and Chronic Disease Study (554,562); Study of Women's Health Across the Nation (521); and Women's Health Initiative Observational Study (528,568). We included five studies using registry data (529,540,541,546,550,569). The size of the studies varied from 335,216 participants (540) to 28 (557) participants with a median study size of 847 (563). The follow up ranged from 12 months (558,564) to 28 years (532).

Figure 19 - *Flow of included studies*

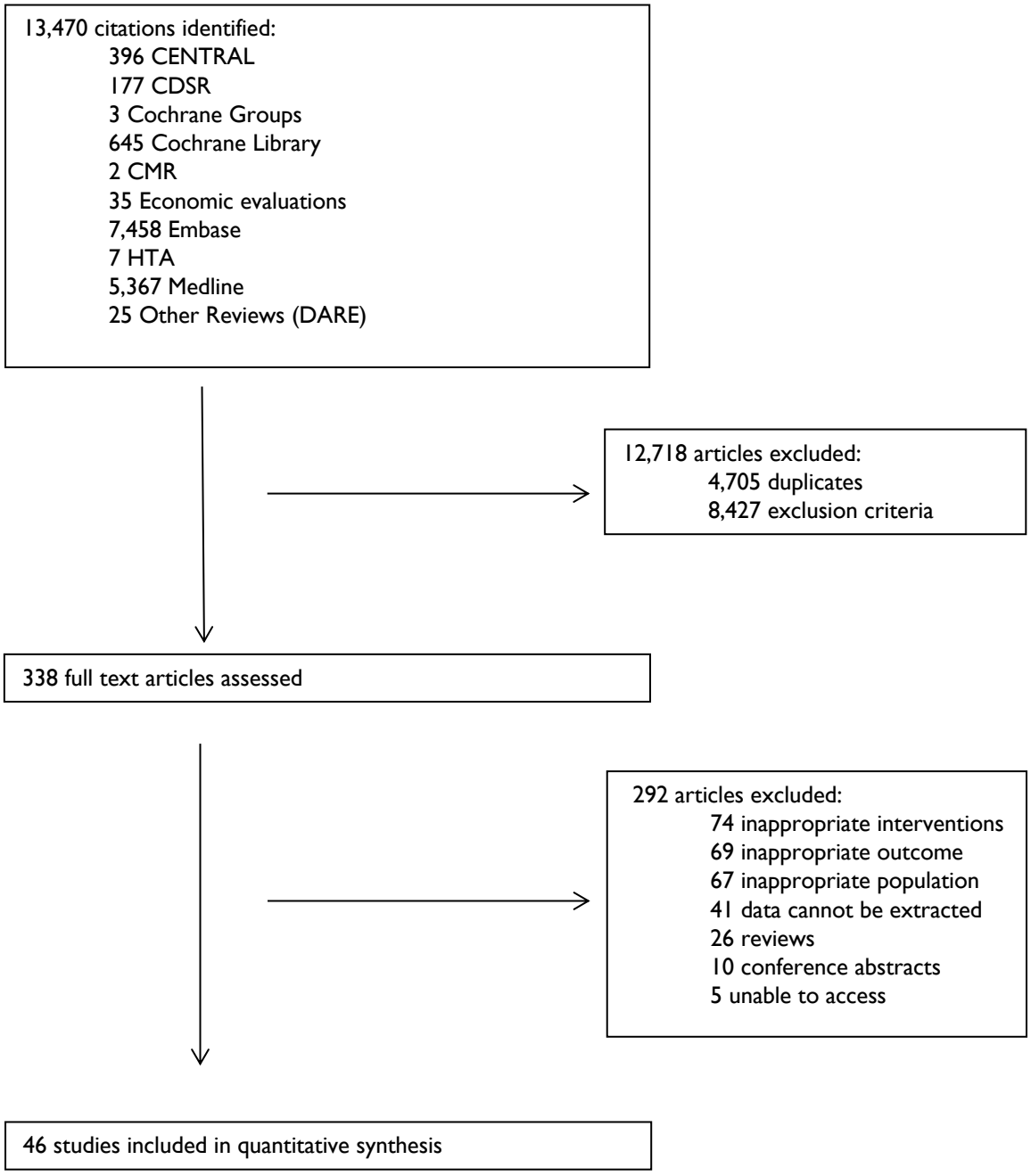


Table 20 - *Study Characteristics*

Study			Population					Exposure	Outcome						
Author Year (Country)	**Study Design**	**Data Source** Recruitment Exposure assessment Outcome assessment Follow up n years (range)	**Participants (n)**	**Inclusion Criteria**	**Exclusion Criteria**	**HRT⁺ use**	**Confounders adjusted for**	**Intervention**	**Mortality**	**Cardiovascular***	**Malignancy**	**Musculoskeletal****	**Neurological**	**Depression / Anxiety**	**Other**
MORTALITY AND CARDIOVASCULAR DISEASE															
Colditz 1987 (USA)	Cohort	The Nurses' Health Study. Biennial questionnaire of self-reported exposure and outcome. Follow up 6 years (1976-1982).	16,563	Married registered nurses living in 11 American States. Aged 30-55 in 1976. Menopausal.	Diagnosis of coronary heart disease at entry. Unknown exposure.	Unadjusted data.	Not specified.	Hysterectomy n=8,061 Hysterectomy & BSO n=8,502		✔					
Gordon 1978 (USA)	Cohort	The Framingham Study. Biennial examination of women assessing exposure and outcome. Follow up 24 years.	544	Women in the Framingham Study. Aged 29 to 62 in 1948.	Not described.	Unadjusted data.	Not specified.	Hysterectomy n=146 Hysterectomy & BSO n=398		✔					

Howard 2005 (USA)	Cohort	Women's Health Initiative Observational Study. Annual self-reported exposure and outcome. Mean follow up 5.1 years.	36,924	Postmenopausal women, 40 clinical centres in the USA. Aged 50-79 years in 1994-1998.	Migration within 3 years. Terminal illness. Inability to provide informed consent.	Unadjusted data.	Age, ethnicity, family history, income, education , body mass index, white blood cell count, physical activity, dietary saturated fat. Hypertension, diabetes, high cholesterol, smoking, peripheral arterial disease, and deep venous thrombosis histories. Baseline cardiovascular disease, angina, or congestive heart failure.	Hysterectomy n=18,688 Hysterectomy & BSO n=18,236	✔	✔	✔				
Ingelsson 2010 (Sweden)	Cohort	The Swedish Classification of Operations and Major Procedures & Swedish Inpatient Register: Medical record linkage for recruitment, exposure and outcome assessment. Median follow up 10.4 years (1973-2003).	184,441	Hysterectomy for benign disease between 1973 and 2003.	Outcome present at study entry. Exposure for malignant disease. Exposure less than 18 years of age. Death before follow up. Migration during follow up.	Unadjusted data.	Age, calendar time, county, socio-economic status.	Hysterectomy n=156,305 Hysterectomy & BSO n=24,910		✔					
Jacoby 2011 (USA)	Cohort	Women's Health Initiative Observational Study. Annual self-reported outcome and exposure. Mean follow up 5.1 years.	25,448	Postmenopausal women, 40 clinical centres in the USA. Aged 50-79	Migration within 3 years. Terminal illness. Inability to provide informed	Adjusted data.	Age, ethnicity, education, medical insurance, current health care provider, parity, body mass index,	Hysterectomy n=11,194	✔	✔	✔	✔			

				years in 1994-1998.	consent. Unknown exposure. Previous malignancy. Family history of ovarian malignancy.		HRT use, smoking, alcohol , exercise, hypertension, diabetes mellitus, high cholesterol levels requiring medication, personal history of myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, stroke or family history of myocardial infarction or stroke.	Hysterectomy & BSO n=14,254							
Luoto 1995 (Finland)	Cross-sectional	Mini-Finland Health Survey. Self-reported exposure. Medical record linkage for outcome. Surveyed in 1977-1980.	226	Women aged 30-95 years old having a hysterectomy (between 1944 and 1979).	Unconfirmed hysterectomies and missing information on cardiovascular risk factors.	Adjusted data.	Age, body mass index, interaction between age and body mass index, HRT, cholesterol, triglycerides, glucose, smoking, alcohol, education.	Hysterectomy n=163 Hysterectomy & BSO n=55		✔					
Palmer 1992 (USA)	Case-control	Multi-centre state wide recruitment, Massachusetts, USA. Medical record linkage of outcome. Self-reported exposure.	480	Cases: Aged 45-69. Hospitalisation for a first nonfatal myocardial infarction. Control: Age and geographical	Unable to contact by telephone.	Adjusted data.	Smoking, hypertension, high cholesterol, diabetes mellitus, family history of myocardial infarction, body mass index, coffee and alcohol consumption, patient and	Case: Hysterectomy n=87 Case: Hysterectomy & BSO n=157		✔					

				ly matched. No history of myocardial infarction.			spouse education, HRT use, occupation, age at menarche, parity, age at first birth, menopausal status.	Control Hysterectomy n=96 Control Hysterectomy & BSO n=140							
Parker 2009 (USA)	Cohort	The Nurses' Health Study. Self-reported biennial postal questionnaire of exposure and outcome. Follow up 24 years.	29,380	Married registered nurses living in 11 American States. Aged 30-55 in 1976. No diagnosis of gynaecological cancer.	USO or partial oophorectomy. Unknown ovarian status at time of hysterectomy. Prior history of an outcome of interest. Oophorectomy before hysterectomy. Missing information on past oral contraceptive use.	Adjusted data.	Age, age at hysterectomy, diabetes, high blood pressure, hypercholesterolemia, family history of myocardial infarction before age 60 years, body mass index in 1976, smoking status, use of HRT, duration of oral contraceptive use, parity, alcohol intake, physical activity, aspirin use.	Hysterectomy n=13,035 Hysterectomy & BSO n=16,345	✔	✔	✔	✔			✔
Parker 2013 (USA)	Cohort	The Nurses' Health Study. Self-reported biennial postal questionnaire of exposure and outcome. Follow up 28 years.	30,117	Married registered nurses living in 11 American States. Aged 30-55 in 1976. Hysterectomy for benign disease.	History of other cancers, coronary heart disease, stroke or pulmonary embolus. USO or partial oophorectomy. Unknown age or ovarian status at time of hysterectomy	Adjusted data.	Age, age at hysterectomy, body mass index in 1976, smoking status, use of HRT, past duration of oral contraceptive use, parity, physical activity, alcohol intake, aspirin use.	Hysterectomy n=13,203 Hysterectomy & BSO n=16,914	✔	✔	✔				

					. Oophorectomy not at time of hysterectomy.										
Rosenburg 1981 (USA)	Case-control	The Nurses' Health Study. Medical record linkage for outcome. Self-reported exposure.	1,264	Married registered nurses living in 11 American States. Born from 1921-1946. Case: Hospitalised for myocardial infarction in 1965-1977. Control: Age matched. No history of myocardial infarction. Known menopause status.	Case: Unknown type of menopause. Hospitalised in year that menopause occurred.	Adjusted for length of use.	Age at hospitalisation, area of residence, year of hospitalisation, length of use of post-menopausal HRT, use of oral contraceptive in month prior to hospitalisation, obesity, smoking, history of hypertension, diabetes, high cholesterol, angina and parental myocardial infarction before age 50.	Case: Hysterectomy n=50 Case: Hysterectomy & BSO n=48 Control Hysterectomy n=769 Control Hysterectomy & BSO n=397		✔					
Van der Schouw 1996 (Netherlands)	Cohort	DOM Project for breast cancer screening. Self-reported exposure. Medical record linkage for outcome. Median follow up 10 years.	1,678	Aged 50-65 at enrolment. Residents of Utrecht, Netherlands.	Use of HRT.	Women using HRT excluded from study.	Age at menopause.	Hysterectomy n=791 Hysterectomy & BSO n=887		✔					
MALIGNANCY															

Boggs 2014 (USA)	Cohort	Black Women's Health Study. Biennial patient questionnaire for exposure. Medical record linkage for outcome. Follow up 1995-2011.	9,132	At least 40 years old during follow up period. No previous malignancy before enrolment.	History of cancer at baseline, family history of ovarian cancer, oophorectomy without hysterectomy.	Adjusted data.	Age, body mass index, menopausal hormone use, smoking history, education, geographic region, family history of breast cancer.	Hysterectomy n=4,576 Hysterectomy & BSO n=4,556			✔					
Brinton 1981 (USA)	Case-Control	Breast Cancer Detection Demonstration Project. Self-reported exposure. Medical record linkage for outcome. Follow up 4 years (1973-1977).	624	Asymptomatic women aged 35-74 from 29 centres in the USA.	Not described.	Stratified by HRT use and regime.	Age, type of menopause, HRT use.	Case: Hysterectomy n=156 Case: Hysterectomy & BSO n=158 Control Hysterectomy n=133 Control Hysterectomy & BSO n=177			✔					
Cape 1999 (Canada)	Cohort	Inpatient and outpatient recruitment. Medical record linkage of exposure. Medical record linkage of outcome assessment. Mean follow up 7-8 years.	266,514	Women aged 15-64 who had gynaecological surgery from 1979-1993.	Operation within 6 months of malignancy diagnosis.	Not specified.	Not specified.	Hysterectomy n=187,838 (479) Hysterectomy & BSO n=77,676 (328)			✔					
Chan 2014	Cohort	Inpatient recruitment. Medical record linkage of exposure.	52,716	Women aged 18-84 undergoing benign gynaecologi	Previous malignancy, pre-malignancy abnormal	Not specified.	Age at intervention, ethnicity.	Hysterectomy n=22,051 (31)			✔					

(USA)		Medical record linkage of outcome assessment. Follow up 18 years (1988-2006).		cal surgery. Median age 45.	cervical smear or malignancy diagnosis within 90 days of surgery.			Hysterectomy & BSO n=30,665 (13)							
Cui 2014 (USA)	Case-control	Inpatient recruitment (case), community recruitment (control). Medical record linkage of outcome. Self-reported exposure. Recruitment 2001-2011.	1,097	Case: Women aged 25-75, primary breast cancer, Nashville Tennessee. Control: Random geographical community matched controls.	Case: Previous malignancy. Control: Not described.	Stratified by never used HRT and ever used HRT.	Age, education.	Case: Hysterectomy n=213 Case: Hysterectomy & BSO n=336 Control: Hysterectomy n=177 Control: Hysterectomy & BSO n=371			✔				
Duell 2004 (USA)	Case-control	Inpatient recruitment (case), community recruitment (control). Structured interviews assessment of exposure. Medical record linkage of outcome. Recruitment 1995-1999.	599	Case: Women with primary adenocarcinoma of the exocrine pancreas. Aged 21-85. Control: Community based. Age, race and geographically matched to cases.	Case: Not described. Control: Not described.	Unadjusted data.	Age, education, smoking.	Case hysterectomy n=83 Case hysterectomy & BSO n=47 Control hysterectomy n=313 Control hysterectomy & BSO n=156			✔				

Duell 2010 (10 European countries)	Cohort	Community recruitment. Self-reported questionnaires for exposure. Outcome assessment via national cancer registry. Mean follow up 8.7 years.	335,216	Women aged 35-70 between 1992-1998.	Widespread malignancy at the time of recruitment.	Unadjusted data.	Age, location, smoking, education, body mass index, calorie-adjusted food intakes.	Hysterectomy = 159,380 person-years Hysterectomy & BSO = 86,508 person years			✔				
Falconer 2015 (Sweden)	Cohort	National database recruitment; Swedish cancer register. Surgical medical record linkage for exposure and outcome. Mean follow up 23.1 years.	135,374	Women aged 16-74 undergoing operation between 1973-1996.	Previous primary ovarian malignancy at recruitment.	Not specified.	Age, education, parity.	Hysterectomy n=98,026 (278) Hysterectomy & BSO n=37,348 (7)			✔				
Gallagher 2013 (China)	Cohort	Community recruitment. Self-reported exposure. Medical record linkage for outcome. Mean follow up 9.3 person-years (1989-2000).	248	Women born 1925-1958 working in textile factories in Shanghai.	Not described	Not specified.	Age, smoking.	Hysterectomy n=160 (38) Hysterectomy & BSO n=88 (24)			✔				
Gaudet 2014 (USA)	Cohort	Cancer Prevention Study-II Nutrition Cohort. Biennial self-reported questionnaires to establish exposure and outcome. Median follow up 13.9 years (1992-2009).	25,405	Women aged 50-74 from 21 American States.	Previous malignancy at enrolment. Previous smoker.	Adjusted data.	Age, ethnicity, parity, education, alcohol, smoking, HRT use, menopause, physical activity, body mass index.	Hysterectomy n= 9,655 (1143) Hysterectomy & BSO n=15,750 (1892)			✔				

Helmrich 1983 (USA, Canada, Israel)	Case-control	Inpatient recruitment of cases and controls. Self-reported questionnaire assessing exposure and outcome.	1,187	Case: Women ages less than 70 years with a diagnosis of breast cancer within 1 year. Control: Hospital inpatients less than 70 years with non-breast and non-gynaecological disease.	Previous history of cancer. Admission for gynaecological disease.	Not specified.	Age at cancer, age at menopause.	Case: Hysterectomy n=123 Case: Hysterectomy & BSO: 99 Control: Hysterectomy n=436 Control: Hysterectomy & BSO n=529			✔				
Holly 1994 (USA)	Case-control	Surveillance, Epidemiology, and End Results program. Structured interviews for exposure. Hospital record linkage for outcome.	269	Case: Aged 25-59. Diagnosis of cutaneous melanoma between 1981-1987. Control: Aged 25-59. Identified via random-digit dialling. Aged and geographic matching to cases.	Not described	Stratified by HRT use.	Age, education.	Case: Hysterectomy n=85 Case: Hysterectomy & BSO n=58 Control: Hysterectomy n=80 Control: Hysterectomy & BSO n=46			✔				

Luoto 2003 (Finland)	Cohort	The Mini-Finland Health Survey. Medical record linkage for exposure and outcome using national database: Finnish Cancer Registry. Mean follow up 6 years (1986-1995).	85,200	Total or subtotal hysterectomy with and without BSO between 1986–1995.	Not described.	Not specified.	Not specified.	Hysterectomy n=58,721 (80) Hysterectomy & BSO n=26,479 (31)			✔				
Mack 1999 (USA)	Case-control	Consecutive community recruitment (1980-1983) of cases and controls. Self-reported exposure at interview. Medical record linkage for outcome.	50	Case: Age15-54 with histological diagnosis of thyroid cancer. Control: Community matched by age and race.	Non-English-speaking, non-white women.	Adjusted data.	Hormone use, thyroid disease.	Case: Hysterectomy n=18 Case: Hysterectomy & BSO n=14 Control: Hysterectomy n=15 Control: Hysterectomy & BSO n=3			✔				
Nichols 2010 (USA)	Case-control	Inpatient recruitment (cases) and community recruitment (controls) from 1992–1995. Structured interview assessment of exposure. Medical record linkage of outcome.	2,796	Case: 50-79 years old with invasive breast cancer. Control: age and location matched community controls.	Case: Previous cancer. Control: Previous cancer.	Adjusted data.	Age, geographical location, age at menarche, duration of oral contraceptive use, parity, age at first delivery, HRT use, body mass index, mammography, family history of breast cancer.	Case hysterectomy n=476 Case hysterectomy + BSO n= 885 Control hysterectomy n=474			✔				

								Control hysterectomy & BSO n=961							
Parazzini 1997 (Italy)	Case-control	Inpatient recruitment of cases and controls. Self-reported exposure. Medical record linkage for outcome.	1,103	Case: 22-74 years old, median age 54, and cancer of the breast histologically confirmed within 1 year. Control: Inpatients admitted with acute illness. 20-74 years old (median age 55). Age and geographically matched.	Case: Not described. Control: Hospital admission for gynaecological or neoplastic disease.	Not specified.	Age, calendar year of follow up, education, parity, age at delivery, family history.	Case hysterectomy n=235 Case hysterectomy & BSO n=268 Control hysterectomy n=299 Control hysterectomy & BSO n=301			✔				
Schairer 1997 (Sweden)	Cohort	Swedish National Cancer Registry. Medical record linkage of exposure and outcomes. Mean follow up 12.2 years (1965-1987).	15,844	All women undergoing hysterectomy and/or oophorectomy for benign disease in Uppsala region of Sweden 1965-1983.	No previous malignancy at time of operation.	Not specified.	Not specified.	Hysterectomy n=data unavailable Hysterectomy & BSO n=data unavailable			✔				

MUSCULOSKELETAL DISORDERS															
Fletcher 2013 (Jamaica)	Cross- sectional	University Hospital of the West Indies. Medical record linkage of exposure. Self-reported outcomes at interview.	403	Afro-Jamaican women. Case: Community based premenopausal women aged over 40 years. Hysterectomy from 1980-2000. Control: Community based, age matched controls. No hysterectomy or hysterectomy with BSO.	Not described.	Not specified.	Not specified.	Case: Hysterectomy n=252 Case: Hysterectomy & BSO n=151				✔			✔
Forsmo 2001 (Norway)	Cross-sectional	Community-based recruitment. Exposure by self-reported postal health questionnaire. Outcome by health examination and bone densitometry.	112	Perimenopausal and postmenopausal women aged 50-59 years old.	No data on menopause	Unadjusted data.	Not specified.	Hysterectomy n=91 Hysterectomy & BSO n=21				✔			
Grainge 2001	Cross-sectional	Early Postmenopausal Interventional Cohort study at the UK centre and 20 community based women.	130	Postmenopausal aged 45-61 years. In good	Hormone replacement within the last 3 months.	Unadjusted data.	Not specified.	Hysterectomy n=95				✔			

(UK)		Interviewer administered questionnaire for exposure. Medical record linkage for outcomes.		health. Lumbar spine anatomy suitable for bone densitometry.	Disease likely to have affected bone turnover. Current use of medication which may affect bone metabolism. Allergy to bisphosphonates. Gastrointestinal symptoms within the previous year. Excessive body weight. No more than 10% of women were permitted to have a spinal bone mineral density below 0.8g/cm^2.			Hysterectomy & BSO n=35							
Hreshchyshyn 1988 (USA)	Cross-sectional	Self-reported exposure. Medical record linkage for outcomes.	82	Ambulatory white women aged 35-65. Ambulatory. Normal lumbar spines.	Traumatic fractures of any kind. Cessation of menses before age 37.	Data representing no HRT use selected.	Not specified.	Hysterectomy n=37 Hysterectomy & BSO n=45				✔			
Johansson 1993 (Sweden)	Cross-sectional	Intervention Trial, part of the gerontological study. Self-reported exposure at interview. Medical record linkage for outcomes.	40	Aged 70.	Hormone replacement. Users of cortisone, heparin, phenytoin, vitamin D, L-thyroxine. Women with	Women using HRT excluded from study.	Socio-economic factors, body mass index, smoking.	Hysterectomy n=22 Hysterectomy & BSO n=18				✔			

					hyperthyroidism.										
Kritz-Silverstein 2004 (USA)	Cohort	Rancho Bernardo Heart and Chronic Disease Study. Self-reported exposure at interview. Medical record linkage for outcomes. Initial (1988-1991) and follow up visit (1992-1995).	447	Aged 60-89 years (average 71 years) at initial interview. Ambulatory.	Change of HT use status between follow up visits. Never menstruated.	Adjusted data.	Age, body mass index, age at menopause, HRT use.	Hysterectomy n=122 Hysterectomy & BSO n=91				✔			
Loizzi 1989 (Italy)	Cohort	Gynaecological clinic outpatient recruitment. Medical record linkage of exposure. Self-reported outcome. 1-6 years postoperatively.	965	Hysterectomy for benign indications between 1982-1987. Mean age at hysterectomy 48.2 years.	Malignant disease.	Unadjusted data.	Not specified.	Hysterectomy n=234 Hysterectomy & BSO n=609				✔			✔
Nakamura 1991 (Japan)	Cross-sectional	Outpatient recruitment. Self-reported questionnaires for exposure. Medical record linkage for outcomes.	161	Women within 4 years post-surgery.	Not described.	Not specified.	Not specified.	Hysterectomy n=75 Hysterectomy & BSO n=86				✔			
Shilbayeh 2003 (Jordan)	Cross-sectional	Recruitment via outpatient primary health clinics in and random telephone survey. Self-reposted exposure by interviewer-administered questionnaire. Medical record linkage for outcomes.	28	Attending outpatient clinics or randomly selected via telephone from 2000-2002. Mean age 53 years.	Pregnancy and lactation.	Unadjusted data.	Not specified.	Hysterectomy n=21 Hysterectomy & BSO n=7				✔			
Smeets-Goevaers 1998	Cross-sectional	The Eindhoven Perimenopausal Osteoporosis Study. Self-reported questionnaire for exposure.	1,117	White Dutch women aged 46-54 years	Failure to provide relevant information. Unable to	Data representing all women	Not specified.	Hysterectomy n=777				✔			

(The Netherlands)		Medical record linkage for outcomes.		(average 50 years).	measure bone mineral density.	using HRT.		Hysterectomy & BSO n=340							
Tuppurainen 1995 (Finland)	Cross-sectional	Kuopio Osteoporosis Risk Factor and Prevention Study. Postal questionnaire for exposure. Medical record linkage for outcomes.	265	Perimenopausal women aged 47-57 years (in 1989).	Past or current use of hormone replacement. Hip deformities; marked spine osteophytes or deformities	Unadjusted data.	Not specified.	Hysterectomy n=195 Hysterectomy & BSO n=70				✔			
ANXIETY AND DEPRESSION															
Aziz 2005 (Sweden)	Cohort	Multi-centre study, inpatient recruitment. Medical record linkage for exposure. Self-reported outcome. Preoperative and one year follow up.	362	Last menstruation less than 12 months ago, sexually active women of a partner relationship. Aged 45-55 at entry. Hysterectomy for benign indication, operated on between 1996 and 1999.	A mental or physical disease that would interfere with the studied parameters. Previous medical help for sexual problems.	Unadjusted data.	Not specified.	Hysterectomy n=217 Hysterectomy & BSO n=106						✔	✔
Chen 2013 (China)	Cross-sectional	Community recruitment. Medical record linkage for exposure. Self-reported outcome at interview.	593	Aged 45-60 years. At menopausal transition or less than 5 years post menopause. Capable of verbal communication.	Persistent smoking or alcohol habit, long term use of oral contraceptives or NSAID drugs. Heavy manual job. History of HRT use.	Women with history of HRT use excluded from study.	Not specified.	Hysterectomy n=337 Hysterectomy & BSO n=256						✔	

				Hysterectomy for benign indication with no malignancy revealed by post-operative pathology, between 2003 and 2008.	Pre-existing pelvic floor dysfunction or psychiatric disorder.										
Farquhar 2005 (New Zealand)	Cohort	Inpatient recruitment. Self-reported questionnaires for exposure. Self-reported outcomes. Assessed one week before surgery, then post-surgery at 6 weeks, 6 months, and annually for 3 years.	314	Younger than 46 years.	Malignancy of the cervix, endometrium or ovary.	Not specified.	Not specified.	Hysterectomy n=257 Hysterectomy & BSO n=57						✔	✔
Gibson 2012 (USA)	Cohort	Study of Women's Health Across the Nation. Self-reported exposure. Outcome by questionnaire, Centre for Epidemiologic Studies Depression Score), blood samples and physical examination. Baseline interview (1996-1997) followed annually for up to 10 years.	177	Aged 42-52 years. Not pregnant, not using HRT. One or more menstrual cycles in the 3 months prior to the interview.	Not described.	Adjusted data.	Hysterectomy status, time since final menstrual period or surgery, geographical location, ethnicity, education, menopausal status, age, body mass index, self-rated health, antidepressant use, HRT use.	Hysterectomy n=76 Hysterectomy & BSO n=101						✔	
Haines 1993 (Hong Kong)	Cohort	Inpatient recruitment. Medical record linkage for exposure. Self-reported outcome.	66	Aged over 35, undergoing laparotomy for any indication.	Not described.	Not specified.	Not specified.	Hysterectomy n=33						✔	✔

		Follow up postoperatively on day of discharge and outpatient visits at least 6 weeks postoperatively.						Hysterectomy & BSO n=33							
Kritz-Silverstein 1994 (USA)	Cross-sectional	Rancho Bernardo Heart and Chronic Disease Study (enrolment and interviews in 1972-1974). Self-reported exposure at interview. Self-reported outcome.	463	Postmenopausal aged 50-89 (average age 70.1).	Women uncertain if their ovaries had been removed. Reported uterine or ovarian cancer.	Adjusted data.	Age, HRT use, age at menopause.	Hysterectomy n=240 Hysterectomy & BSO n=223						✔	
Legorreta 2013 (Mexico)	Cross-sectional	National Climateric Survey of the Mexican Association for the Study of the Climacteric. Exposure by interviewer-administered questionnaire. Self-reported outcome at interview	847	Aged 40-59 years (mean 49.5 years). Attending gynaecological clinics across Mexico for any indication.	Significant mental or physical impairment.	Unadjusted data.	Not specified.	Hysterectomy n=762 Hysterectomy & BSO n=85						✔	✔
Rohl 2008 (Australia)	Cohort	Maryland Women's Health Study. Depressive symptoms. Exposure and outcome by interviewer-administered questionnaire for outcome (Profile of Mood States Survey). Baseline and 12 month follow up.	1,047	Premenopausal women in Australia having surgery in 1992-1993. Benign indications and findings at time of surgery.	Malignancy diagnosed at the time of surgery.	Unadjusted data.	Age, parity, ethnicity, income, endometriosis, smoking.	Hysterectomy n=614 Hysterectomy & BSO n=433						✔	
NEUROLOGICAL															
Imtiaz 2014 (Finland)	Case-control	Residing in Finland on 31st December 2005. Finish National Registry Exposure from coded registry linkage	4013	Aged 42–101 years. Case: Women with Alzheimer's disease	Case: Surgeries after Alzheimer's disease diagnosis.	Adjusted data.	Adjusted for use and duration of HRT and modified Charlson	Case Hysterectomy n=1274							✔

		Outcome from coded registry linkage Community controls		decline in cognition supported by neuroimaging or cerebrospinal fluid findings. Confirmed by a geriatrician or a neurologist. Control: Matched with a control by age, gender and region of residence.	Control: Not described.		comorbidity index.	Hysterectomy & BSO n=611 Control Hysterectomy n=1426 Hysterectomy & BSO n=702							
Total			1,272,071												

+ Hormone replacement therapy

* Cardiovascular outcomes include: coronary heart disease incidence and deaths, myocardial infarction incidence and deaths, angina incidence, cardiovascular disease incidence and deaths, stroke incidence and deaths.

** Musculoskeletal outcomes include: osteoporosis, osteopenia, bone mineral density, fracture.

BSO; bilateral salpingo-oophorectomy

USO; unilateral salpingo-oophorectomy

Table 21 - *Quality Assessment*

	Newcastle Ottawa Score (risk of bias)		
Author, Year (Country)	**Selection**	**Comparability**	**Outcome**
Mortality and cardiovascular disease			
Colditz, 1987 (USA)	Medium	Medium	Medium
Gordon, 1978 (USA)	High	Medium	High
Howard, 2005 (USA)	Medium	Medium	Low
Ingelsson, 2010 (Sweden)	Low	Medium	Low
Jacoby, 2011 (USA)	Medium	Low	Low
Luoto, 1995 (Finland)	Medium	Low	Medium
Palmer, 1992 (USA)	Low	Low	Medium
Parker, 2009 (USA)	High	Low	Medium
Parker, 2013 (USA)	Medium	Low	Medium
Rosenburg, 1981 (USA)	Medium	Medium	Medium
Van der Schouw, 1996 (The Netherlands)	Medium	Medium	Low
Malignancy			
Boggs, 2014 (USA)	Medium	Medium	Medium
Brinton, 1981 (USA)	High	Low	Medium
Cape, 1999 (Canada)	Low	Medium	Low
Chan, 2014 (USA)	Low	Medium	Low
Cui, 2014 (USA)	Low	Medium	Medium
Duell, 2004 (USA)	Medium	Medium	Medium

Duell, 2010 (Europe)	Medium	Medium	Low
Falconer, 2015 (Sweden)	Low	Medium	Low
Gallagher, 2013 (China)	High	Medium	Low
Gaudet 2014 (USA)	Medium	Low	Medium
Helmrich, 1983 (USA)	High	High	High
Holly, 1999 (USA)	Medium	Medium	Medium
Luoto, 2003 (Finland)	Medium	Medium	Low
Mack, 1999 (USA)	High	Medium	High
Nichols, 2010 (USA)	Low	Low	Medium
Parazzini, 1997 (Italy)	Medium	Medium	Medium
Schairer, 1997 (Sweden)	Medium	Medium	Low
Musculoskeletal			
Fletcher, 2013 (Jamaica)	Low	Medium	Low
Forsmo, 2001 (Norway)	Medium	High	Medium
Grainge, 2001 (UK)	Low	Medium	Medium
Hreshchyshyn, 1988 (USA)	Medium	Medium	Medium
Johansson, 1993 (Sweden)	Low	Low	Medium
Kritz-Silverstein, 2004 (USA)	Medium	Medium	Medium
Loizzi, 1989 (Italy)	Medium	High	Medium
Nakamura, 1991 (Japan)	Medium	High	Medium
Shilbayeh, 2003 (Jordan)	Medium	High	Medium
Smeets-Goevaers, 1988 (The Netherlands)	Medium	High	High
Tuppurainen, 1995 (Finland)	Medium	Medium	High

Depression and anxiety			
Aziz, 2005 (Sweden)	Medium	High	Low
Chen, 2013 (China)	Low	Medium	Low
Farquhar, 2005 (New Zealand)	Medium	High	Low
Gibson, 2012 (USA)	Medium	Low	Low
Haines, 1993 (Hong Kong)	Medium	High	Medium
Kritz-Silverstein, 1994 (USA)	Medium	Medium	Low
Legorreta, 2013 (Mexico)	Medium	High	High
Rohl, 2008 (Australia)	Medium	Medium	Low
Neurological			
Imtiaz 2014 (Finland)	Low	Low	Low

Comparator descriptions were restricted to hysterectomy with ovarian conservation. Studies measured various outcomes (Table 20) including mortality (528,531,532,568), cardiovascular disease (528–534,566–569), coronary heart disease (528,529,532,567,569), stroke (528,532,569), osteoporosis (520,556,565), sexual dysfunction (558,559), depression (521,560,562–564), anxiety (559,561,563), and malignancy (517,535–550).

Outcomes were routinely assessed by hospital records (including death certificate) (517,520,522,525,530,533–542,545,546,548–553,555–557,562,564,565,567,569), and self-reported questionnaires or interview (521,524,528,531,532,543,544,547,554,558–561,563,566,568). Some outcomes were measured shortly after the procedure; others

were measured at several times over the course of follow up period. The studies included assessed the following disease domains, cardiovascular disease, musculoskeletal disorders, malignancy, mortality, anxiety, depression and neurological disease.

Cardiovascular outcomes were assessed in 11 studies (528–534,566–569) with five outcomes reported: cardiovascular disease; cardiovascular death; coronary heart disease; myocardial infarction; and stroke. Six studies were included for meta-analysis (528,532,534,567,569).

Musculoskeletal disease outcomes were assessed by ten studies (520,522,524,525,552–557,562,565) with four outcomes reported: bone mineral density; fracture; osteopenia; and osteoporosis. The methodology used for reporting outcomes varied greatly: five studies (525,553,554,556,565) used bone mineral density across four sites; three studies (524,525,555) reported the number of women with osteoporosis; and three studies (528,531,556) reported fracture occurrence. Five studies were included for meta-analysis (520,528,531,556,565).

Twenty-one studies (517,528,531,532,535–550,568) examined the relationship with malignancy. These studies reported five outcomes; all cancer; breast cancer; colorectal cancer; lung cancer, and ovarian cancer. Meta-analysis was performed by study type stratifying by type of malignancy. Eight studies (517,528,531,535,537,541–543) were included for meta-analysis.

All-cause Mortality was assessed in four studies (528,531,532,568) with all-cause mortality as the only outcome reported. Two studies were included for meta-analysis (528,532).

Eight studies (521,558–564) reported anxiety and depression with one comparable outcome; diagnosis of anxiety and depression (yes/no), reported by two studies

(559,563). The reporting of depression and anxiety varied, with some studies reporting patient event rate (560–562), and others using a change in validated depression rating scale (521,558,559,563,564). Four studies were included for meta-analysis (559,562–564).

We identified only one study examining neurological disorders, Alzheimer's disease (551); we therefore did not perform a meta-analysis of this outcome.

Studies confounded for the following variable during analysis: age (528,529,531,532,535,536,538–543,545,548,549,551,554,562,564,568,569); age at first birth (530,548,549); age at intervention (517,531,532,562); age at menarche (530,548); age at outcome (533,544); alcohol (528–532,543); antidepressant use (521); BMI (521,528–533,535,540,543,548,553,554,568)'; cardiovascular medications (568); deep vein thrombosis (568); diabetes (528,531,533); dietary saturated fat (568); duration of contraceptive use (531–533,547,548); education (521,528,529,535,538–541,543,545,549); endometriosis (564); ethnicity (517,521,528,543,568); family history of outcome (528,530,531,535,548,549,568); food intake (540); geographical location (521,533,535,540,548,551,569); HRT use (521,528,529,531–533,536,543,547,548,551,554,564); hypercholesterolaemia (528,530–533,568); hypertension (528–531,533,535); Income (564,568); mammography (548); medical insurance (528); menopausal status (521,530,543,562); parity (528,530–532,541,543,548,549,564); peripheral arterial disease (568); physical activity (528,531,532,543,568); self-rated health (521); smoking (528–533,535,540,542,543,553,564,568); socioeconomic status (553,569); and White Blood Cell count (568).

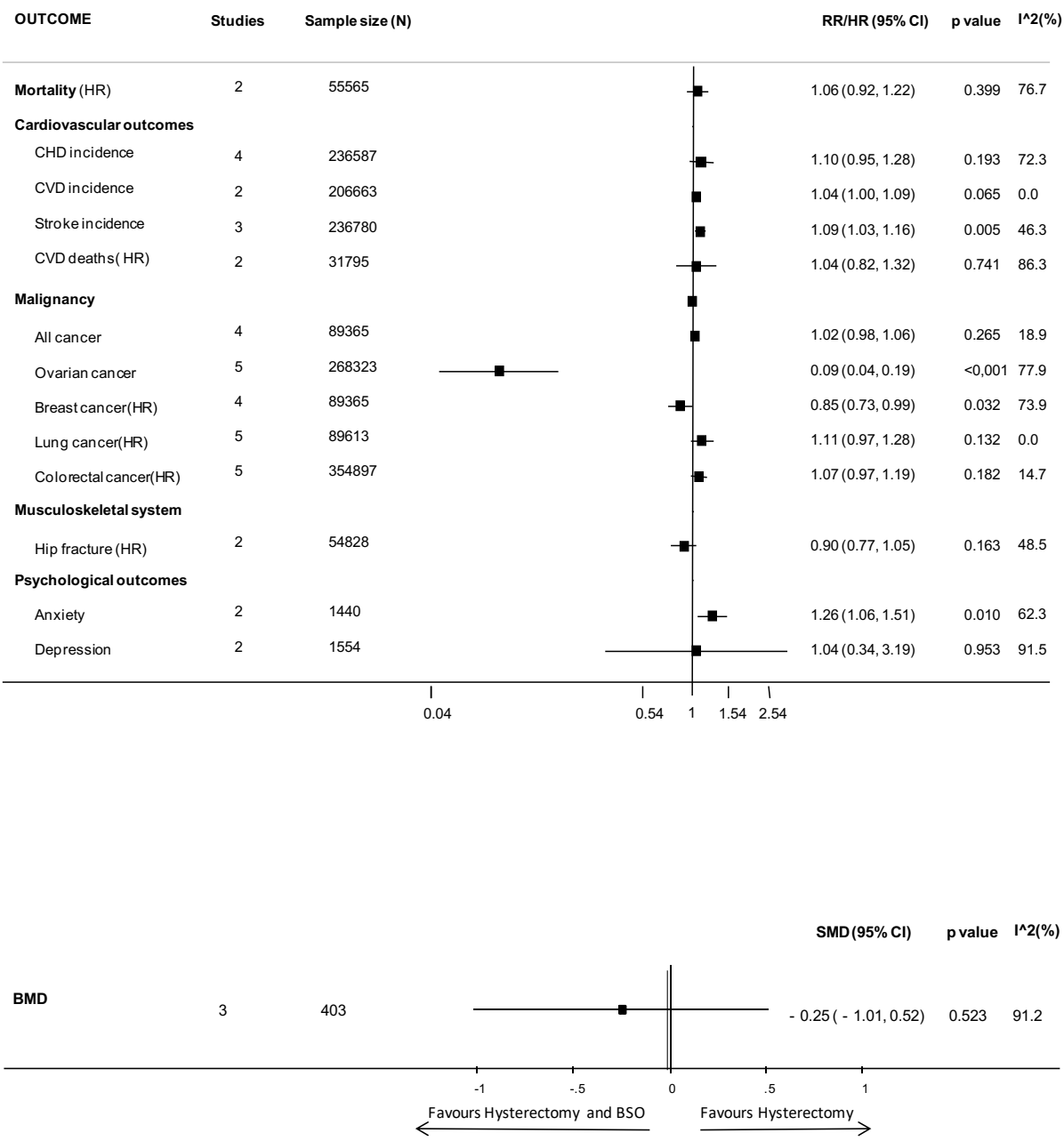
Quality of included studies varied (Table 21): 30 (64%) of studies had low or medium risk of bias across all domains (517,521,524,528–530,532–535,537–539,541,543,545,546,548–554,559,560,564,566,568,569). Twelve (24%) of the studies

(517,520,524,530,537,538,541,548,551,553,559,569) had low risk of bias for study selection; 30 (63%) studies (521,522,525,528,529,533–535,539,540,543,545,546,549,550,552,554–558,560–566,568) had medium risk; and six studies (13%)(531,536,542,544,547,567) had high risk of bias. For comparability, 11 (22%) studies (521,528–531,536,543,548,551,553) had low risk, 28 (69%) studies (517,520,522,524,533–535,537–539,541,542,545–547,549,550,552,559,560,562,564,566–569) had medium risk, and nine (19%) studies (525,544,555–558,561,563,565) had high risk of bias. The risk of bias for outcome assessment was low in 19 (39%) studies (517,521,524,528,534,537,540–542,546,550,551,558–560,562,564,568,569), medium in 24 (48%) studies (520,529–533,535,536,538,539,543,545,548,549,552–557,561,565,566), and high in 6 (13%) studies (522,525,544,547,563,567).

Hysterectomy and bilateral oophorectomy compared to hysterectomy alone significantly increases the risk of stroke (figure 20), RR 1.09 (95% CI 1.03 – 1.16), and anxiety, RR 1.26 (95% CI 1.06 – 1.51). There are significant reductions in risk of ovarian cancer, RR 0.09 (95% CI 0.04 – 0.19), and breast cancer, hazard ratio 0.85 (95% CI 0.73 – 0.99) (figure 20). There were non-significant increases in risk for the following outcomes: coronary heart disease 1.10 (95% CI 0.95 – 1.28); cardiovascular disease 1.04 (95% CI 1.00 – 1.09); mortality 1.06 (95% CI 0.92 – 1.22); all cause malignancy 1.02 (95% CI 0.98 – 1.06); lung cancer 1.13 (95% CI 0.97 – 1.31); colorectal cancer 1.07 (95% CI 0.97 – 1.19); and cardiovascular disease deaths 1.04 HR (95% CI 0.82 – 1.33). There were non-significant reductions in risk for the following outcomes: hip fracture 0.89 RR (95% CI 0.77 – 1.05); and bone mass density -0.25 SMD (95% CI -1.02 – 0.52). There were no differences noted for risk of developing depression 1.03 RR (95% CI 0.34 – 3.19) (20). Event rates for hysterectomy and hysterectomy with bilateral oophorectomy are reported in Table 22. Heterogeneity was high across all outcome domains: mortality 76.7%;

cardiovascular outcomes 0-86.3%; malignancy 0-77.9%; musculoskeletal system 48.5-91.2%; and psychological outcomes 62.3-91.5%.

Figure 20 - *Summary forest plot*



BMD: bone mass density, BSO: bilateral salpingo-oophorectomy , CHD: coronary heart disease, CVD: cardiovascular disease, CI: confidence Interval, RR: relative Risk, HR: hazard ratio

Table 22 - *Event Rate*

Author, Year (Country)	Participants (n)	Intervention hysterectomy (n)	Event rate hysterectomy (n)	Event rate per 1000 for hysterectomy	Intervention hysterectomy and bilateral salpino-oophorectomy (n)	Event rate hysterectomy and bilateral salpingo-oophorectomy (n)	Event rate per 1000 for hysterectomy and bilateral salpingo-oophorectomy	Mortality	Cardiovascular*	Malignancy	Musculoskeletal**	Neurological	Depression / Anxiety	Other
Forest plot A: Coronary heart disease incidence														
Gordon 1978 (USA)	544	146	7	47.9	398	14	35.1		✔					
Ingelsson 2010 (Sweden)	184,441	156,305	3,774	24.1	24,910	610	24.5		✔					
Jacoby 2011 (USA)	25,448	11,194	298	26.6	14,254	405	28.4	✔	✔	✔	✔			
Parker 2013 (USA)	30,117	13,203	169	12.8	16,914	289	17.6	✔	✔	✔				

Luoto 1995 (Finland)	226	163	19	116.6	55	10	181.8		✔					
Forest plot B: Cardiovascular disease incidence														
Ingelsson 2010 (Sweden)	184,441	156,305	8,871	56.8	24,910	1,492	59.9		✔					
Jacoby 2011 (USA)	25,448	11,194	1,171	104.6	14,254	1,513	106.1	✔	✔	✔	✔			
Forest plot C: Stroke incidence														
Ingelsson 2010 (Sweden)	184,441	156,305	5,098	32.6	24,910	882	35.4		✔					
Jacoby 2011 (USA)	25,448	11,194	263	23.4	14,254	341	23.9	✔	✔	✔	✔			
Parker 2013 (USA)	30,117	13,203	112	8.5	16,914	192	11.4	✔	✔	✔				

Forest plot D: Cardiovascular disease deaths														
Parker 2013 (USA)	30,117	13,203	281	21.2	16,914	481	28.4	✔	✔	✔				
Van der Schouw 1996 (Netherlands)	1,678	791	Not specified	-	887	Not specified	-		✔					
Forest plot D: Myocardial infarction incidence														
Rosenburg 1981 (USA)	1,264	-	Case 50 Control 769	-	-	Case 48 Control 397	-		✔					
Palmer 1992 (USA)	480	-	Case 87 Control 96	-	-	Case 157 Control 140	-		✔					
Forest plot D: All-cause mortality														
Jacoby 2011 (USA)	25,448	11,194	673	60.1	14,254	857	60.1	✔	✔	✔	✔			
Parker	30,117	13,203	1,749	132.5	16,914	2,850	168.5	✔	✔	✔				

2013 (USA)														
Forest plot D: All malignancy														
Jacoby 2011 (USA)	25,448	11,194	951	85.0	14,254	1,205	84.5	✔	✔	✔	✔			
Parker 2009 (USA)	30,117	13,035	1,716	131.6	16,345	2,183	133.6	✔	✔	✔				
Boggs 2014 (USA)	9,132	4,576	411	89.8	4,556	469	102.9			✔				
Gaudet 2014 (USA)	25,405	9,655	1,143	118.4	15,750	1,892	120.1			✔				
Forest plot D: Ovarian cancer														
Jacoby 2011 (USA)	25,448	11,194	951	85.0	14,254	1,205	84.5	✔	✔	✔	✔			

Parker 2009 (USA)	30,117	13,035	99	7.6	16,345	5	0.3	✔	✔	✔				
Chan 2014 (USA)	52,716	22,051	31	1.4	30,665	13	0.4			✔				
Falconer 2015 (Sweden)	135,374	98,026	278	2.8	37,348	7	0.2			✔				
Gaudet 2014 (USA)	25,405	9,655	1,143	118.4	15,750	1,892	120.1			✔				
Forest plot D: Breast cancer														
Jacoby 2011 (USA)	25,448	11,194	309	27.6	14,254	430	30.2	✔	✔	✔	✔			
Parker 2009 (USA)	30,117	13,035	775	59.5	16,345	895	54.8	✔	✔	✔				
Boggs 2014	9,132	4,576	180	39.3	4,556	183	40.2			✔				

(USA)														
Gaudet 2014 (USA)	25,405	9,655	419	43.4	15,750	715	45.4			✔				
Forest plot D: Lung cancer														
Jacoby 2011 (USA)	25,448	11,194	99	8.8	14,254	129	9.1	✔	✔	✔	✔			
Parker 2009 (USA)	30,117	13,035	170	13.0	16,345	284	17.4	✔	✔	✔				
Boggs 2014 (USA)	9,132	4,576	43	9.4	4,556	76	16.7			✔				
Gallagher 2013 (China)	248	160	38	237.5	88	24	272.7							
Gaudet 2014 (USA)	25,405	9,655	58	6.0	15,750	111	7.0			✔				

Forest plot D: Colorectal cancer														
Jacoby 2011 (USA)	25,448	11,194	89	8.0	14,254	126	8.8	✔	✔	✔	✔			
Parker 2009 (USA)	30,117	13,035	154	11.8	16,345	234	14.3	✔	✔	✔				
Boggs 2014 (USA)	9,132	4,576	44	9.6	4,556	62	13.6			✔				
Cape 1999 (Canada)	266,514	187,838	497	2.6	77,676	328	4.2			✔				
Gaudet 2014 (USA)	25,405	9,655	116	12.0	15,750	219	13.9			✔				
Forest plot D: Osteoporosis														
Forsmo 2001 (Norway)	112	91	Not applicable	-	21	Not applicable	-				✔			

Grainge 2001 (UK)	130	95	Not applicable	-	35	Not applicable	-				✔			
Nakamura 1991 (Japan)	161	75	Not applicable	-	86	Not applicable	-				✔			
Forest plot D: Anxiety														
Chen 2013 (China)	593	337	49	145.4	256	57	222.7						✔	✔
Haines 1993 (Hong Kong)	66	33	3	90.9	33	5	151.5						✔	
Legorreta 2013 (Mexico)	847	762	392	514.4	85	33	388.2						✔	
Forest plot D: Depression														
Chen 2013 (China)	593	337	61	181.0	256	92	359.4						✔	✔

Farquhar 2005 (New Zealand)	314	257	53	206.2	57	23	403.5						✔	
Kritz-Silverstein 1994 (USA)	463	240	19	79.2	223	28	125.6						✔	✔
Legorreta 2013 (Mexico)	847	762	499	654.9	85	31	364						✔	
Rohl 2008 (Australia)	1,047	614	93	151.5	433	39	90.1						✔	

The range in NNH varied according to the prior baseline risk for the population (Table 23). Amongst high risk populations for stroke (baseline risk = 35%) the NNH was 32 hysterectomies and BSO for one additional stroke. This increased to 222 hysterectomies with bilateral oophorectomy for one stroke in a low risk (baseline risk = 5%) population. The NNH for an additional case of anxiety (baseline risk = 5.9%) was 65 hysterectomies with bilateral oophorectomy. The NNT to prevent one case of ovarian cancer (baseline risk = 2.5%) was 44. The NNT to prevent one case of breast cancer (baseline risk = 12%) was 56 hysterectomies with bilateral oophorectomy. To prevent one case of ovarian cancer it is estimated that there will be an additional 1.4 episodes of stroke amongst high risk women and 0.7 episodes of anxiety. To prevent one case of breast cancer there will be an estimated 1.8 additional stroke episodes and 0.9 episodes of anxiety.

Table 23 - *Number need to treat and harm.*

Outcome	**Scenario**	**Lifetime risk**	**Relative risk**	**NNH**
Anxiety	All	5.92%	1.26	65
Stroke	Low risk	5%	1.09	222
	Moderate risk	20%		56
	High risk	35%		32
				NNT
Breast cancer	All	12%	0.85	56
Ovarian cancer	All	2.5%	0.09	44

Main findings

Our meta-analysis generated quantitative estimation of the health risks following hysterectomy, with and without oophorectomy. In women undergoing hysterectomy with bilateral oophorectomy for benign gynaecological disease there was a significant increase in stroke and anxiety with concurrent reductions in breast and ovarian cancers. There were increases associated with cardiovascular disease, coronary heart disease, all cause malignancy, bowel malignancy, and lung malignancy associated with bilateral oophorectomy at the time of hysterectomy which did not reach statistical significance. Our review, with the essential quantitative information about long term health risks associated with hysterectomy and oophorectomy, will help in counselling to ensure that the 2,000 women each day who undergo hysterectomy are fully informed of the risks and benefits of a concurrent bilateral oophorectomy.

Strengths

To our knowledge this is the first prospectively registered systematic review to address health outcomes associated with bilateral oophorectomy at the time of benign hysterectomy. We conducted a comprehensive search strategy, employed a robust methodology, and used advanced statistical syntheses. Using the Newcastle-Ottawa scale, we assessed study quality and risk of bias. We believe that this study is the most comprehensive systematic review and meta-analysis evaluating the health risks of bilateral oophorectomy at the time of hysterectomy, including 1,665,063 women.

Limitations

There are no RCTs which address this question despite the large population which undergo this procedure each year with a lack of robust evidence to guide practice has limited previous Cochrane reviews of this topic (518). Observational studies including cohort and case-control were included in this systematic review. Expanding our search

of the literature to include observational studies has been essential to our review. It can be argued that there are disadvantages to meta-analysing observational data. However, we used a thorough search strategy, without language restrictions, and a comprehensive selection process to ensure all relevant studies were captured. Individual studies were assessed and carefully considered prior to inclusion.

Demographic variants including location, ethnicity, and age, varied across studies. We aimed to control for the effect of HRT in our analysis. Due to inconsistency of outcome reporting, we were limited in our meta-analysis. We were unable to explore the effects on blood pressure or BMI due to poor outcome reporting quality (529,570–572). Due to variation in outcome measures used to evaluate bone mineral density(522,525,552–554) we were unable to compare data. The presentation of data within studies prohibited sub-group analysis by indication for hysterectomy or age at hysterectomy. The possible protective effects of post-menopausal ovaries were not analysable due to heterogeneous outcome reporting. We were unable to make an assessment on whether age, HT use, or menopause status has an influence on the outcomes evaluated. This could be addressed in future research through an individual patient data meta-analysis. The unwarranted variation in outcome and outcome measure reporting within studies has been highlighted as a major limitation within women's health research (384). This is being addressed by the CoRe Outcomes in Women's and Newborn health (CROWN) initiative which advocates for the development of a core outcome set for every women's health disease and procedure (382).

There was a large amount of statistical heterogeneity, so we used random effects meta-analyses, which produces more conservative CIs. This is acknowledged to only partly remove effects of heterogeneity (573). We believe that to combine this data would provide a more clinically useful result than to include a smaller number of homogeneous studies.

Interpretation

Hysterectomy with bilateral oophorectomy significantly increases a patients' risk of future stroke and anxiety compared to hysterectomy alone. There is concomitant reduction in risk of hormonal dependent cancers of the breast and ovary. This offers clinicians and patients a greater insight into health risks associated with bilateral oophorectomy at the time of hysterectomy. This can aid shared decision making for patients and clinicians prior to surgery together with the iatrogenic health sequelae of prophylactic bilateral oophorectomy.

There have been significant trends towards rising BMI in females that may result in the development of cardiac disease. The results of this study indicate both significant and multiple non-significant increases in cardiac diseases with bilateral oophorectomy at the time of hysterectomy. This important, and growing, risk factor should play a role in clinician-patient decision making prior to hysterectomy. Patients at higher risk of future stroke should have appropriate counselling of the detrimental and contributory effects that bilateral oophorectomy may have on their health in later life. Following natural menopause, the ovaries continue to produce testosterone and androstenedione which are converted to oestrogen in peripheral tissues (574). The surgical removal of healthy ovaries without clinical indication prohibits the protective effects that post-menopausal ovaries provide. The non-significant trend towards a reduction in hip fractures and higher BMD is difficult to explain. This may be explained via greater clinician vigilance and use of medical therapies to prevent osteoporotic morbidity in later life.

To address the need for bilateral oophorectomy at the time of hysterectomy, more effective screening tools for ovarian cancer need to be developed. The prompt initiation of treatment for early stage ovarian cancer leads to cure rates as high as 90% to 95% while vague and non-specific symptoms lead to presentation with a late stage diagnosis in 75% of patients. At this advanced stage, ovarian cancer has a low cure rate. An effective and affordable screening test that allows early diagnosis, when ovarian cancer

is most treatable, could eliminate the justification for bilateral oophorectomy at the time of hysterectomy (575).

We are not aware of any other systematic review that assesses long term outcomes specifically relating to ovarian removal or conservation at hysterectomy for benign disease. On the basis of our findings, women undergoing hysterectomy for benign disease, should be informed of the small but significant increase in cardiovascular and psychiatric risks associated with bilateral oophorectomy.

9.6 CONCLUSION

Current recommendations surrounding the choice of ovarian removal or conservation at hysterectomy for benign indications are limited. Hysterectomy and bilateral oophorectomy compared with hysterectomy alone significantly increase a range of risks for patients, which need to be balanced against possible benefits. Gynaecologists need to provide women with advice on the choices they face at the time of hysterectomy with both acute and chronic risks. An individual patient data meta-analysis in the future will produce more robust evidence synthesis regarding the risks and benefits of bilateral oophorectomy at the time of benign hysterectomy.

CHAPTER 9:

TO EVALUATE THE ROLE OF MUSIC TO AID POST-OPERATIVE RECOVERY FOLLOWING ENDOMETRIOSIS SURGERY

10.1 ABSTRACT

Background

Music is a non-invasive, safe and inexpensive intervention that can be easily delivered to patients. This systematic review aimed to evaluate music to as aid to postoperative recovery following endometriosis surgery.

Methods

RCTs in any language of adult patients undergoing surgery for endometriosis were included. Any form of music initiated before, during or after surgery was compared to standard care or other non-drug interventions. Medline (1946-Dec 2015), Embase (1947-Dec 2015), CINAHL (1960-Dec 2015), and Cochrane Central (1898-Dec 2015) were searched, using MESH and keyword search terms: endometriosis, endometrio*, gynaecolog*, gynecolog*, music, music therapy, surg*, operat*, recovery, recuperation, rehabilitation, convalescence, post-op*. Inclusions, data extraction and quality assessment were in duplicate. Meta-analysis with RevMan (5.2), with standardised mean differences (SMD) and random effects models, and STATA for meta-regression were used. (Prospero-CRD42013005220).

Results

No studies assessed endometriosis surgery and the criteria was expanded to include all gynaecological surgery. 10 studies were included assessing 1056 participants with size varying between 26 - 372 participants. Choice of music, timing and duration varied. Comparators included routine care, headphones with no music, and recording of operating room noise. Postoperatively music reduced anxiety (SMD -0.56 (95% CIs (95%CI) -1.02 to -0.02). There were non-significant improvements in pain SMD -0.37 (95%CI -0.80 to 0.06), and analgesia use SMD -0.32 (95%CI -0.96 to 0.33) and

increased patient satisfaction SMD 0.52 (95%CI -0.98 to 2.03), and length of stay SMD -0.19 (95%CI –0.71 to 0.32)).

Conclusions

This systematic review demonstrates that music improves anxiety following gynaecological surgery. We are unable to make meaning conclusions regarding the efficacy of music within benign gynaecological surgery to improve pain, satisfaction, and length of stay. Due its low cost and low risk profile music should be encouraged to all patients undergoing operative benign gynaecological procedures.

10.2 INTRODUCTION

Surgical procedures are common and represent the gold standard for diagnosing endometriosis. Endometriosis affects one in ten women worldwide and is characterised by pain and subfertility. Following initial surgical diagnosis and treatment an estimated 40-50% will have symptom recurrence within five years (576). Many women with endometriosis require multiple surgical procedures to control and manage this enigmatic disease. Current surgical recovery strategies, such as Enhanced Recovery (577–579) recommend numerous successful perioperative interventions within this package. Some preoperative strategies, such as patient education and nutritional additives, have been seen to reduce postoperative pain requirements and improve satisfaction levels (577–579) but many non-pharmacological interventions are yet to be evaluated or incorporated.

Music has an historic foundation within medical care and was first described as an adjunct to patient recovery during operations in the early twentieth century by Kane et al. (580) this was later advocated by Florence Nightingale (581). Music has a demonstrable impact on the emotions and neurophysiology (582–584).

The delivery of pre-recorded music through headphones, musical pillows or background sound systems is an alternative inexpensive, non-invasive, and safe intervention in the post-operative setting (585). Music has been investigated in the context of recovery from invasive and minimally invasive operative procedures with numerous RCTs affirming positive effects on patients' postoperative recovery (586,587).

Previous systematic reviews have investigated music and its role as an aid to specific surgical procedures (12,13) and all surgical procedures combined (590) without analysing gynaecological procedures individually.

Endometriosis is a chronic disease characterised by pain. Music is not currently being

used during the surgical pathway for managing the disease. Barriers to implementation include a lack of: budget, research dissemination and integration of the intervention in daily practice (591).

We aim to review the effectiveness of music to improve postoperative recovery following surgery for endometriosis.

10.3 METHODS

We developed and registered a protocol for this systematic review (CRD42016017631). The pre-defined inclusion criteria were RCTs in any language with adult female patients undergoing endometriosis surgery which was later expanded to include all gynaecological operations. Any form of music initiated before, during or after surgery was compared to standard care or any other non-drug interventions such as massage, undisturbed rest or relaxation. Outcomes of interest were: postoperative pain, analgesia requirement, anxiety, infection rates, wound healing, costs, length of stay, and satisfaction with care. Analgesia use included any opioids or NSAIDs. If both were reported, opioid use was used in the meta-analyses. The outcomes were measured up to six weeks postoperatively.

The following databases were searched: Medline (1946-December 2015), Embase (1947-Decmber 2015), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1960-December 2015), and Cochrane Central (1898-Dec 2015). The following search terms were used; music, music therapy, surg*, operat*, recovery, recuperation, rehabilitation, convalescence, post-op*. Both MESH terms and keywords were used. Reference lists of relevant reviews were checked for additional studies. All relevant titles and abstracts were transferred to Endnote Web for assessment. Where no includable trials were available for the laparoscopic treatment of endometriosis, we chose to expand the search to all gynaecological procedures.

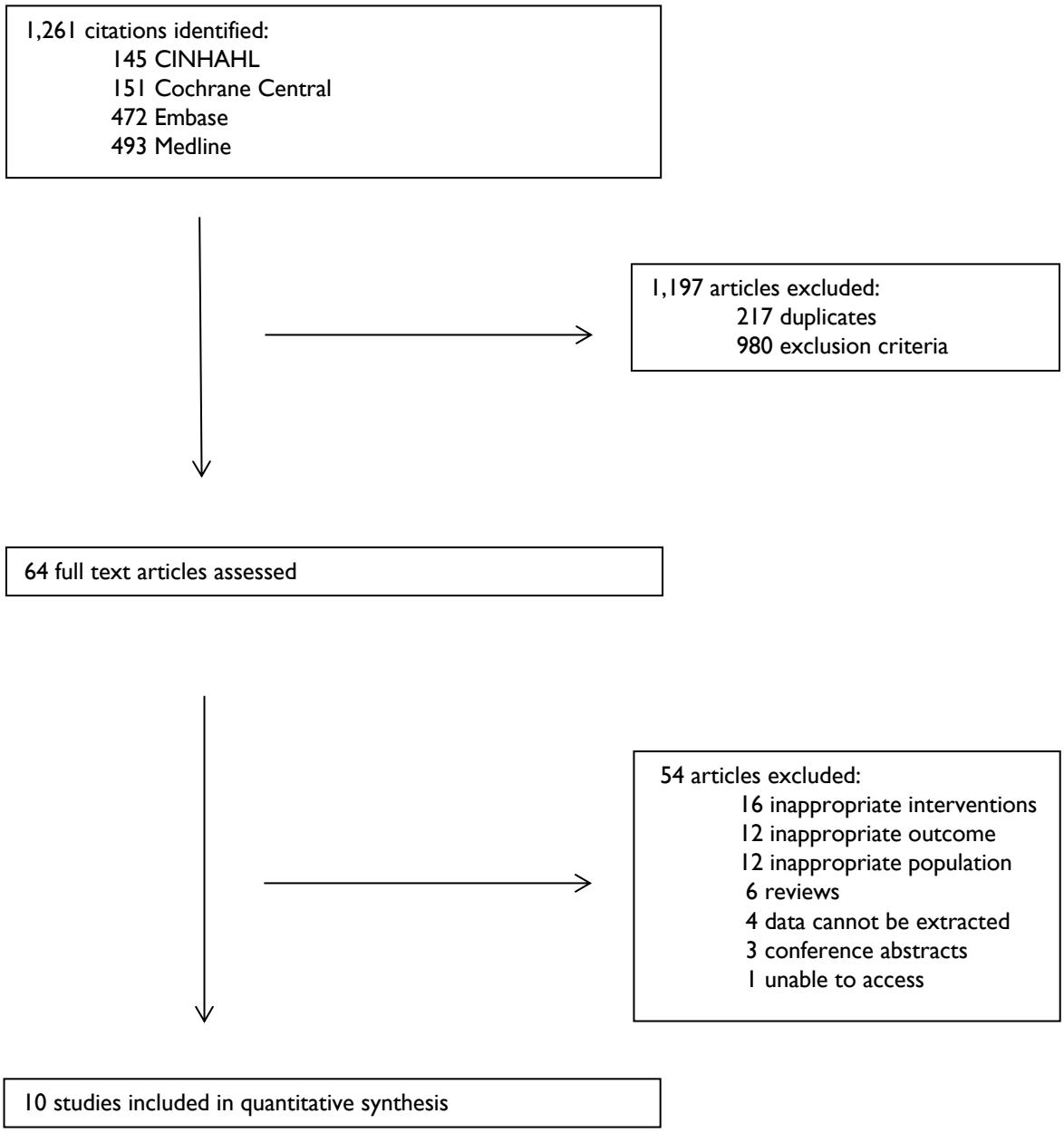
Two reviewers (JH and MH) checked study eligibility. Both independently extracted data from studies using a standardised, pre-designed extraction form in Microsoft Excel 2007. Disagreements were resolved through discussion or referral to a senior reviewer (JMD). Quality of included studies was assessed using criteria set by The York Centre for Reviews and Dissemination (592); focusing on randomisation, allocation concealment, presence of blinding, explanation of withdrawals and presence or absence of intention-to-treat analysis.

We tabulated the characteristics and results of all the included studies; analysis was quantitative. Where standard errors or ranges were provided, SDs were calculated using standard formulae. Review Manager (version 5.2, The Cochrane Library) was used for meta-analyses. We used random effects models because of heterogeneity of participants and interventions. All outcomes were continuous measures and we used standardised mean differences (SMD) where the outcomes had differing measurement scales.

10.4 RESULTS

Searches retrieved 1,261 titles and abstracts. No trials evaluated the use of music to aid post-operative recovery following surgery for endometriosis. We included 10 RCTs including 966 women evaluating music as an aid to post-operative recovery from benign gynaecological surgery. (figure 21).

Figure 21 – *Flow of included studies*



Characteristics of included studies are found in table 24. The size of the studies varied between 26 - 372 participants, and they underwent a variety of different surgical procedures ranging from minor endoscopic interventions to open hysterectomy. Most studies only included elective procedures. Choice of music could be by patient or researcher. Patients chose a wide variety of styles. Researchers determined single types of music such as Chinese classical music,or gave patients' choice from a list of six or more styles. Most were of a soothing quality. Delivery could be by headphones or music pillows for patients only to hear, or loudspeakers which could also be heard by the medical team. When music was delivered by headphones, it was often at a sufficiently low level that patients could still communicate easily. Timing could be pre, intra or postoperative, or a combination. The music could be played when patients were awake or anesthetised. Duration of music varied between a few minutes to repeated episodes over several days. Comparator descriptions varied, and included routine care, headphones with no music, white noise, and undisturbed bed rest. Duration and timing was normally similar to the interventions. Outcomes included postoperative pain, analgesia requirement, anxiety, length of stay, and satisfaction with care. None of the RCTs measured infection rates, wound healing or costs. Some outcomes were measured during or just after the procedure, others were measured at multiple times during the hospital stay.

Table 24 - *Characteristics of included trials*

Author (year)	Number of Participants (n)		Control Group	Procedure	General Anaesthesia	Music type	Patient Choice	Timing of delivery	Duration of Music
	Intervention	Control							
Agwu & Okoye (2006)	50	50	Routine Care	HSG	No	Patient's own	Yes	Intraoperative	Duration of procedure
Angioli (2015)	185	187	Routine Care	Hysteroscopy	No	Pop, Jazz, Classical, or Rock	Yes	Intraoperative	Duration of procedure
Guerrero (2011)	54	47	Routine Care	Surgical management of miscarriage	No	Patient choice	Yes	Intraoperative	Duration of Procedure
Ikonomidu (2004)	29	26	Blank CD	Laparoscopic Sterilisation	Yes	Pan flutes	No	Pre and post operative periods	30 minutes
Johnson (2012)	43	43	Headphones only	Gynaecological surgery	Yes / No	Country Jazz or New Age	Yes	Pre operative	Until Anaesthetised
Migneault (2004)	15	15	Routine Care	Open Gynaecological Surgery	Yes	Classical, jazz, new age, or Piano	Yes	Intraoperative	Intraoperative only
Mullooly (1988)	14	14	Routine Care	Hysterectomy	Yes	Instrumental	No	Day 2 post operative	10 minutes
Nilsson (2001)	30	28	CD of Operating room noise	Hysterectomy	Yes	Soothing sounds of the sea	No	Intraoperative	Intraoperative only
Wu (2012)	13	13	Routine Care	Termination of pregnancy	No	Patients choice	Yes	Intraoperative	Intraoperative only
Zhang (2005)	55	55	Headphones only	Hysterectomy	Yes	Calming and comforting	Yes	Intraoperative	Intraoperative only

A variety of outcomes were measured (table 25). Pain was usually measured with visual analogue scales (VAS) or numerical rating scales (NRS). An indirect measure of pain was the consumption of analgesia, which varied considerably between the studies including opioid-based drugs such as pethidine, fentanyl, and morphine, and non-steroidal anti-inflammatories such as diclofenac, ibuprofen, and paracetamol.

Table 25 - *Outcomes measured*

Author (year)	Pain score reported	Analgesia use reported	Anxiety score reported	Length of stay reported	Other outcomes reported
Agwu & Okoye (2006)	No	No	Yes, STAI	No	Physiological parameters, HR and BP
Angioli (2015)	Yes, VAS	No	Yes, STAI	No	No
Guerrero (2011)	Yes, VAS	No	Yes, STAI	No	Physiological parameters, HR and BP
Ikonomidu (2004)	Yes, VAS	Yes, mg per drug	No	No	Patient wellbeing, VAS
Johnson (2012)	No	No	Yes, STAI	Yes, time spent in PACU*	No
Migneault (2004)	No	Yes, mg per drug	No	No	No
Mullooly (1988)	Yes, VAS	No	Yes, Likert	No	No
Nilsson (2001)	Yes, VAS	Yes, mg per drug	No	Yes, mobilisation time	Patient wellbeing and nausea, five-grade scale
Wu (2012)	Yes, NRS*	No	Yes, NRS*	No	No
Zhang (2005)	No	No	No	No	Patient satisfaction, VAS

*Not included in numerical meta-analysis result because SD as not reported.

NRS – numerical rating scale. STAI – Stait Trait Anxiety Inventory, HR – heart rate, BP – Blood pressure, VAS – Visual analogue scale, mg – milligram, PACU – Post anaesthetic care unit,

Quality of included studies varied (Table 26) but a number of the studies gave insufficient details to assess all aspects of quality. An intervention such as this cannot be blinded to the patient unless they are under general anaesthesia, but blinding of investigators and outcome assessment would be possible but was not stated in many of the studies. Where music was delivered when the patient was under anaesthesia it was unclear whether the patient knew beforehand to which group they were allocated.

Table 26 - *Risk of Bias (JADAD criteria)*

Author (year)	Was the trial described as randomised?	Did the trial use an appropriate method of randomisation?	Was the trial blinded?	Did the trial use an appropriate method of blinding?	Did the trial account for all patients randomised?
Agwu & Okoye (2006)	Yes	Yes	No	No	Yes
Angioli (2015)	Yes	Yes	No	No	Yes
Guerrero (2011)	Yes	Yes	No	No	Yes
Ikonomidu (2004)	Yes	No	Yes	Yes	Yes
Johnson (2012)	Yes	No	No	No	Yes
Migneault (2004)	Yes	No	Yes	Yes	Yes
Mullooly (1988)	Yes	No	No	No	Yes
Nilsson (2001)	Yes	Yes	Yes	Yes	No
Wu (2012)	Yes	Yes	No	No	Yes
Zhang (2005)	Yes	Yes	Yes	Yes	Yes

The results showed that postoperatively music reduced pain (6 RCTS, SMD –0.37 (95%CI-0.80 – 0.06)) (figure 22), anxiety (6 RCTS, SMD -0.52 (95%CI –1.02 - -0.02)) (figure 23), and analgesia use (3 RCTS, SMD -0.32 (95%CI-0.96 – 0.33)) (figure 23) but there was no difference in length of stay (2 RCTs, SMD -0.19 (95%CI-0.71 – 0.32)) (figure 24). Pain and anxiety SMD outcomes were back-calculated into specific measurements most used in the RCTs.

Figure 22 - *Forest plot of music intervention for pain*

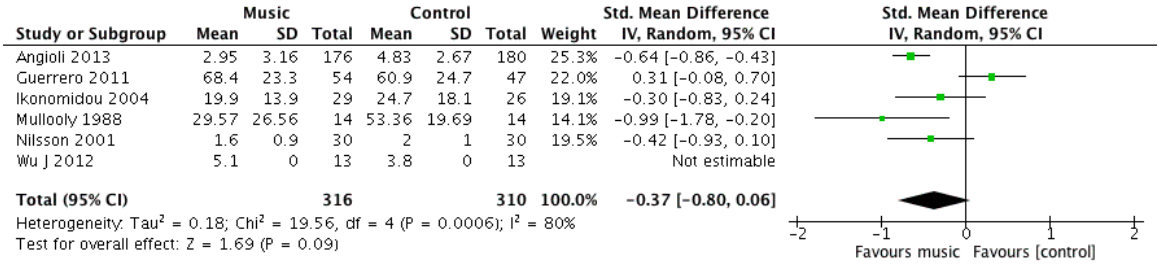


Figure 23 - *Forest plot of music for Anxiety*

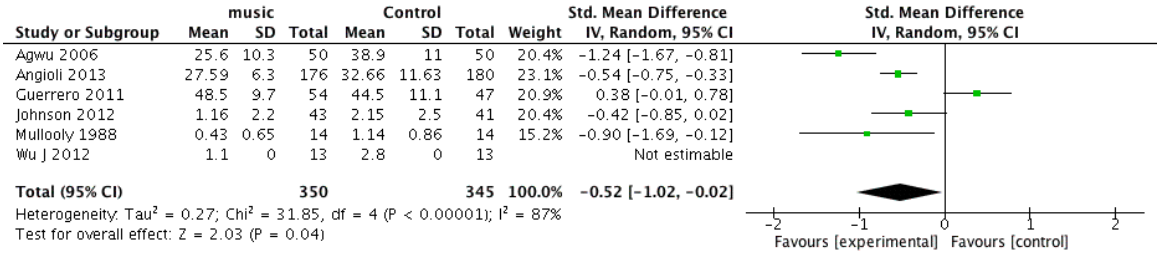
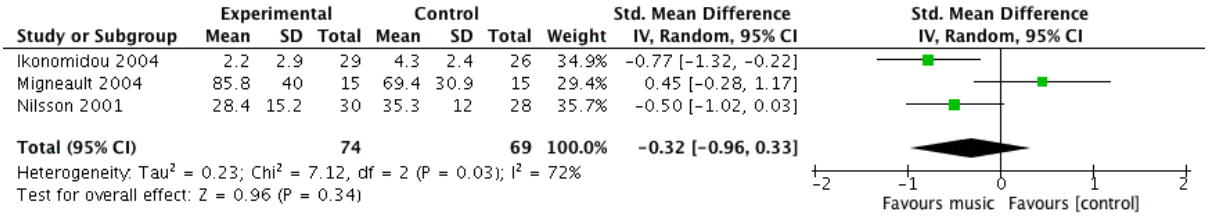


Figure 24 - *Forest plot of music for postoperative analgesia use*

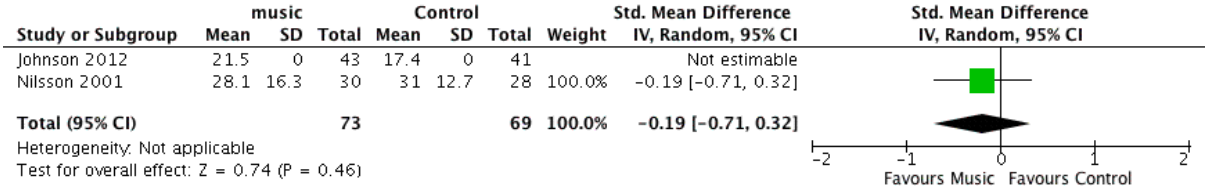


Heterogeneity was high for pain, anxiety and analgesia use, with I^2 varying between 72 - 87%. No RCTs reported wound healing rates, costs, wound infections or serious adverse events. A subgroup analysis by type of control (routine care vs control with attention)

made little difference to the effectiveness of music.

None of the included studies reported side effects. However, some reported that they ensured that the low volume delivered permitted communication with medical teams.

Figure 25 - *Forest plot of music for length of stay*



Statement of principal findings

In this study we demonstrate that playing music in the perioperative setting reduces postoperative anxiety following benign gynaecological surgery. There were similar non-significant trends towards improvement in postoperative pain, length of stay and analgesia requirements. None of the studies investigated the effects of music on infections, wound healing rates, or costs.

Strengths and weaknesses

The strengths of this systematic review and meta-analysis include its originality, robust search strategy, and methodological design. To our knowledge, this is the first systematic review and meta-analysis to examine the effectiveness of music for the postoperative recovery following benign gynaecological surgery. The search strategy was guided by the Cochrane handbook of systematic reviews and there was good agreement between reviewers for the selection of trials with quick resolution of discrepancies.

We were unable to answer the principle study question due to a lack of studies evaluating the effectiveness of music on postoperative recovery following endometriosis surgery. We broadened or inclusion criteria to evaluate all studies performing surgical interventions for benign gynaecological disease. This makes the results more generalisable to a wider gynaecological clinical practice. We combined all studies reporting analgesia use despite studies reporting different analgesics and types of interventions. This introduces clinical heterogeneity. The statistical measures of heterogeneity within this meta-analyses indicated that there was a large amount of statistical heterogeneity in the main analyses for analgesia use, anxiety, and pain. We used a random effects model for meta-analyses which is acknowledged to partially account for the impact of heterogeneity (573). Combining data provides a more clinically

meaningful result than including a narrower range of homogenous studies. The implication of combining clinically heterogeneous studies is that we cannot be sure whether music applies equally to all clinical scenarios however this study was limited by small number of includable studies. Further limitations include the small size of the studies ranging from 26 to 372 participants.

Many of these small RCTs were hard to find in lesser-known journals, which illustrates the benefits of systemic reviews and meta-analysis.

Strengths and weaknesses in relation to other systematic

One strength of this systematic review is the robust methodology. This systematic review includes data and studies used with a previously published systematic review assessing all interventions(590). Prior to this, the most comprehensive systematic review used a vote-counting approach to summarise results only (593). Some of the previous systematic reviews only investigated one outcome, such as anxiety or pain, whereas we report all relevant clinical outcomes. We believe this is the most comprehensive systematic review to date on the use of music to aid recovery following gynaecological surgery, including 626 patients. Our results are similar to Cepeda (2013) in magnitude of effect size (589). We found no side effects reported, as did a recent Cochrane review (587).

Interpretation

The general findings on the beneficial effects of music on the wellbeing of patients undergoing gynaecological surgery are consistent with expectations and the public's perception of music. There are a number of potential mechanisms that could help to explain the effects of music, from the patient's and the medical team's perspective. Modern theories of pain suggest that pain experience is affected by physical and psychological factors. Cognitive activities such as listening to music can influence perceived intensity and unpleasantness of pain, allowing for a reduced pain sensation by

the patient (594). Another potential mechanism could be a reduction in autonomic nervous system activity such as reduced pulse and respiration rate and lower blood pressure (595). For those undergoing general anaesthesia there is some RCT evidence that parts of the brain involved in hearing may sometimes remain perceptive during general anaesthetic (596). For approximately one in a thousand people undergoing general anaesthesia, unwanted intraoperative awareness during the anaesthetic is a risk factor for post-traumatic stress (597). It is unclear at the moment whether intraoperative music might have prevented this by reducing anxiety levels.

Other primary studies and systematic reviews have found that, for medical teams, carers may be more relaxed and attentive (598) where there is music playing that they enjoy, but its use may be inappropriate in certain settings. The medical team may be distracted if music is audible from the patient's headphones. Music may impede communication with patients, particularly during an awake procedure. If patients need to be able to communicate with healthcare workers, bilateral headphone use may be an obstacle. Music and noise have the potential to obstruct other interventions through negatively affecting the surgeon's performance. Because of this, music should not be imposed on the medical team, particularly during the procedure. If medical teams intend to introduce music into the perioperative setting care needs to be taken that music does not interfere with the communication between the medical team (599,600).

Conclusions

Music is a non-invasive, safe and inexpensive intervention that can be delivered easily and successfully in a hospital setting. We recommend that a large RCT would additionally address the issues around heterogeneity. This systematic review and meta-analysis is unable to determine whether music is an effective intervention for endometriosis or all benign gynaecological surgery across all domains of postoperative recovery. Recovery from gynaecological surgery has no particular individually mitigating

features to suspect that the findings of Hole et al are not applicable.

Patients should be able to choose the type of music they would like to hear. The timing of music does not make much difference to outcomes so may be adapted to the individual clinical setting and medical team(590).

This chapter set out to evaluate the role of music in the recovery from endometriosis surgery. There were no studies which answered that question directly and we therefore used gynaecological surgery as a surrogate marker. Endometriosis is different from many other forms of gynaecological disease causing pain in a multitude of different hypothesised mechanisms (601). It is unclear whether all these different pathways would be improved by the listening of music. Further research is required to assess whether the addition of music to the perioperative setting will aid postoperative recovery for patients having endometriosis surgery.

This chapter was based on and adapted from the following peer reviewed publication:

Hole J, Hirsch M, Ball E, Meads C. Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis. Lancet. 2015 Oct 24;386(10004):1659-71.

.

CHAPTER 10:

DISCUSSION AND

PERSPECTIVES

10.1 SUMMARY OF FINDINGS

10.1.1 NON-INVASIVE DIAGNOSTIC ACCURACY TESTS FOR ENDOMETRIOSIS

We evaluated recent studies assessing the accuracy of non-invasive tests for the diagnosis of endometriosis. The commonest marker evaluated was a glycoprotein CA 125. This biomarker had extensive diagnostic accuracy assessment including a meta-analysis with a historic reference standard (visual diagnosis) compared to the current gold standard (biopsy and histopathological analysis). There was limited diagnostic evaluation of the current gold standard. We decided to perform a diagnostic meta-analysis, chapter 2.

10.1.2 THE DIAGNOSITC ACCURACY OF CA-125 FOR ENDOMETRIOSIS IN SYMPTOMATIC WOMEN – A SYSTEMATIC REVIEW AND META-ANALYSIS

Nineteen studies (15 cohort, four case-control), 3163 participants, were included. Bivariate hierarchical models were used to pool accuracy data of 13 studies (2611 participants) using CA 125 ≥30 iu/ml. Pooled specificity was 91% (95% CI 89% - 94%) and sensitivity 51% (95% CI 35% - 66%). CA 125 was significantly more sensitive for the diagnosis of moderate or severe endometriosis compared to minimal disease (62.6% 95% CI 44.6 - 77.6 vs. 24.8% 95%CI 18.8 - 32.1, p value=0.003). CA 125 performs well as a rule in test facilitating expedited diagnosis and ensuring investigation and treatment can be confidently tailored towards the management of endometriosis. Unfortunately, a negative test, CA 125 < 30 iu/ml, is unable to rule out endometriosis.

10.1.3 THE DIAGNOSTIC ACCURACY OF CA-125 FOR ENDOMETRIOSIS IN WOMEN WITH PAIN OR SUBFERTILITY – A PRIMARY STUDY

Fifty-eight consecutive women recruited between October 2013 to March 2015. Women with endometriosis had a higher CA 125 level than those without endometriosis (mean 54.7 +/-71.6 vs 16.2 +/- 8.0). The specificity of CA 125 ≥ 30 iu/ml was 96% (95% CI 81.7 – 99.9%) and sensitivity was 57% (95% CI 37.4 – 74.5%). The positive likelihood ratio for the histological presence of endometriosis with a CA 125 ≥ 30 iu/ml was 15.8 (95% CI 2.3-112) providing a post-test probability of 94% (95% CI 71% - 99%) in women with pelvic pain or subfertility. The area under the curve, 0.85 (95% CI 0.74 – 0.96) indicates high test accuracy. CA 125 ≥ 30 iu/ml is highly predictive of endometriosis in women with symptoms of pain and / or subfertility. CA 125 should be considered as a rule-in test for expediting the diagnosis and management of endometriosis, CA 125 <30 iu/ml is, however, unable to rule out endometriosis.

10.1.4 ASSESSING THE QUALITY OF OUTCOME REPORTING IN ENDOMETRIOSIS TRIALS

A total of 54 RCTS evaluating interventions on 5427 patients were analysed. A total of 164 outcomes were reported using 113 outcome measures. The most commonly reported pain outcome, dysmenorrhoea, was reported by 23 RCTS using 10 outcome measures. The most commonly reported fertility outcome, pregnancy, was reported by 26 RCTS using 3 outcome measures. The quality of outcome reporting was measured using a previously validated tool anchored between 0 (poor outcome reporting) and 6 (excellent outcome reporting). Median outcome reporting quality score was 3 (IQR 2). There was an association between outcome reporting score and methodological quality

and year of publication on multivariate analysis. There was no association between outcome reporting quality and journal impact factor in the year of publication.

Variation in outcome reporting prohibits comparison, combination, and synthesis of data to improve patient care.

10.1.5 ASSESSING THE QUALITY OF INFORMATION AVAILABLE ONLINE FOR ENDOMETRIOSIS

We identified 750 websites, of which 54 were included. Over a third of websites did not attribute authorship and almost half the included websites did not report the sources of information or academic references. No websites provided information assessed as being written in plain English. A minority of websites were assessed as high quality. A single website provided accurate information, evidentlycochrane.net. Available information was, in general, skewed towards the diagnosis of endometriosis. There were 16 credible websites, however the content limitations were infrequently discussed. No website scored highly across all four domains. In the unlikely event that a website reports high quality, accurate, and credible health information it is typically challenging for a lay audience to comprehend. Healthcare professionals, and the wider community, should inform women with endometriosis of the risk of outdated, inaccurate, or even dangerous information online. The implementation of an Information Standard will incentivise providers of online information to establish and adhere to codes of conduct.

10.1.6 ASSESSING THE QUALITY OF GUIDELINES FOR THE DIAGNOSIS AND MANAGEMENT OF ENDOMETRIOSIS

A total of 7 national and international guidelines on the diagnosis and management of endometriosis were retrieved following a systematic search. The quality of guidelines was assessed using a validated assessment tool AGREE-II anchored between 0 (poor quality) 100 (excellent quality). The median quality of guidelines ranged from 4 (French) to 88 (ESHRE). The guideline recommendations were consistent in their clinical guidance but varied significantly in the methodological processes used to develop these statements.

Greater clarity and harmonisation is required in the development of guidelines. It is an unnecessary use of expertise and research funds to develop multiple clinical guidelines for a single condition.

10.1.7 ASSESSING THE MANAGEMENT OF OVARIAN ENDOMETRIOMA IN WOMEN WITH SUBFERTILITY

For patients with subfertility and OEs the ovarian reserve and other fertility parameters should be assessed pre-operatively with subsequent triage for ART treatment or surgery depending on age and ovarian reserve. ART should be considered as the first option where there is evidence of reduced ovarian reserve. This should also be the case for patients with small (<3cm) OEs as these do not appear to affect the outcome of ART.

10.1.8 ASSESSING THE RISKS OF HYSTERECTOMY AND BILATERAL OOPHORECTOMY FOR THE MANAGEMENT OF ENDOMETRIOSIS

We highlighted 48 relevant studies (1,272,071 women). Hysterectomy with bilateral oophorectomy (498,603 women) *vs* without (773,468 women) was associated with increase in stroke (RR 1.09, 95% CI 1.03 – 1.16; baseline risk = 35%; number needed to harm [NNH] = 32) and anxiety (RR 1.26, 95% CI 1.06 – 1.51; baseline risk =5.9%; NNH = 65); and decrease in ovarian cancer (RR 0.09, 95% CI 0.04 – 0.19; baseline risk =

2.5%; number needed to treat [NNT] = 44); and breast cancer (hazard ratio 0.85, 95% CI 0.73 – 0.99; baseline risk = 12%; NNT = 55). The balance of adverse and beneficial health outcomes associated with bilateral oophorectomy should be employed when counselling women concerning benign hysterectomy.

10.1.9 ASSESSING THE ROLE OF MUSIC IN THE RECOVERY OF PATIENTS FOLLOWING ENDOMETRIOSIS SURGERY

No studies assessed endometriosis surgery and the criteria was expanded to include all gynaecological surgery. 10 studies were included assessing 1056 participants with size varying between 26 - 372 participants. Postoperatively music reduced anxiety (SMD -0.56 (95% CIs (95%CI) -1.02 to -0.02) however, there were non-significant improvements in pain SMD -0.37 (95%CI -0.80 to 0.06), and analgesia use SMD -0.32 (95%CI -0.96 to 0.33) and increased patient satisfaction SMD 0.52 (95%CI -0.98 to 2.03), and length of stay SMD -0.19 (95%CI –0.71 to 0.32)). Due its low cost and low risk profile music should be encouraged to all patients undergoing operative benign gynaecological procedures.

10.2 STRENTHS AND LIMITATIONS

This three-part thesis attempted to explore and answer: [1] diagnostic, [2] methodological and [3] therapeutic difficulties within endometriosis research. A series of systematic reviews (chapters 2,4-8), literature review (chapters 1,8) and primary study (chapter 3) had robust methodology with prospective registration adhering to standardised reporting methods. Many of these chapters have undergone thorough scrutiny during the peer review process of publication (appendix 6).

The primary study described in chapter 3 was limited by the number of participants recruited despite being powered this study would have benefitted from greater participant numbers. This study had a two-stage prospective recruitment of participants requiring pre-operative evaluation and further assessment at laparoscopy where they could be excluded. This limited the number of participants included.

The extensive methodological review of information sources available to the three key stakeholders (patients, researchers, and clinicians) in the diagnosis and management of endometriosis could be considered the gold standard for the development of a core outcome set.

We chose not to evaluate publication bias in the two chapters meta-analysing interventions (chapter 9 & 8) due to the low numbers of studies / trials evaluating each outcome.

10.3 IMPLICATIONS FOR CLINICAL PRACTICE

10.3.1 THESIS SECTION 1 (CHAPTERS 1-3)..

The non-invasive diagnosis of endometriosis has been highlighted as research priority since 2009 (111). Despite this, there has been little progress towards the development and use of a sensitive and specific non-invasive diagnostic test to aid speed of diagnosis, confidence with empirical medical treatment, reduce invasive surgical diagnosis, and improve psychological wellbeing of sufferers. Chapters 2 and 3 demonstrate with good replicability that CA-125 has a role within the non-invasive diagnosis of endometriosis. We developed a cut-off level of 30iu/ml from chapter 2 and for methodological consistency we used this to perform test accuracy in chapter 3. A CA-125 blood test result ≥ 30iu/ml provides high positive predictive value of 93-94% amongst women with symptoms of the disease. A negative test result does not exclude endometriosis and around 50% of those with histologically confirmed disease will have a negative test. In the absence of other non-invasive diagnostic tests we recommend that CA-125 be used as a rule in adjunct amongst symptomatic women without ultrasonic evidence of endometriosis.

10.3.2 THESIS SECTION 2 (CHAPTERS 4-6)

The methodological evaluation performed suggests that multidirectional research has led to variation in clinical guidance. The findings indicate that all three consumers (researchers, clinicians and patients) of researcher productivity would benefit from the development and implementation of a core outcome set with endometriosis. The implementation of a minimum set of outcomes that are reported in trails, systematic

reviews and guidelines would facilitate the production of high quality and quantity data that can be compared and contrasted to inform future clinical practice and patient care.

10.3.3 THESIS SECTION 3 (CHAPTERS 7-9)

The surgical management of endometrioma in the context of subfertility remains a difficult and individualised scenario. The risks and benefits of ovarian surgery must be clearly explained to patients as the surgical removal of endometrioma prior to ART is no longer mandatory. Definitive surgery for endometriosis associated pain has considereable long term health risks that need to be considered alongside the beneficial reduction in risk of hormonal mediated malignancies of the ovary and breast.

The use of music in the peri-operative setting reduces anxiety and carries a low risk profile. The provision of patient preferred music during recovery could aid recovery and reduce exposure to analgesics.

10.4 RECOMMENDATIONS FOR FUTURE RESEARCH

10.4.1 CHALLENGES

The biggest challenge facing the future care of women with endometriosis is the unwarranted, unhelpful and often confusing variation in outcome collection and reporting. The development and use of a core outcome set would help to address this challenge as core outcome sets are well-defined, discriminatory, and feasible outcomes routinely collected and reported in randomised trials and systematic reviews. This represents a minimum data set of outcomes selected and prioritised by key stakeholders including healthcare professionals, researchers, and patients. The development and use of a core outcome set does not enforce harmony at the expense of innovation. The existence or use of a core outcome set does not imply that outcomes in an endometriosis trial should be restricted (434). Rather, there is an expectation that the core outcomes will be collected and reported, making it easier for the results of trials to be compared, contrasted and combined as appropriate; while researchers continue to explore other outcomes as well (327,382).

Recognising that the current inconsistency in outcome reporting is a serious hindrance to progress in our specialty, seventy-eight editors of Women's Health journals have formed a consortium to support the development, dissemination, and implementation of core outcome sets (382). CROWN initiative [www.crown-initiative.org] will support the implementation of a core outcome set for endometriosis to increase the value of an initial research effort and ensure all future endometriosis trials report core outcomes, and therefore, routinely contribute data to important research questions.

10.4.2 OBJECTIVES

We aim to produce, disseminate, and implement a core outcome set for endometriosis.

10.4.3 METHODS

PROSPECTIVE REGISTRATION

This study has been prospectively registered with the COMET initiative, the registration number is 691 and is available online [www.comet-initiative.org/studies/details/691].

ETHICAL REVIEW

We asked the advice of the National Research Ethics Service (NRES) about whether this study required ethical review by an NHS Research Ethics Committee, and they advised that this should be considered as service evaluation and development. All participants involved will be asked for their consent before participation in the Delphi study, and all procedures will be conducted according to the Declaration of Helsinki.

STEERING GROUP

An international steering group, including healthcare professionals, researchers, and patients, has been formed to guide the development of this core outcome set.

SCOPE OF THIS CORE OUTCOME SET

The steering group has recommended the core outcome set should apply to clinical studies evaluating therapeutic interventions for women with endometriosis. All therapeutic interventions for endometriosis will be considered regardless of type, setting, or mode of administration. We are not seeking to reach consensus regarding the standardisation of study design including clinical, covariate, and surgical phenotype recording nor specimen collection, processing, and storage. We acknowledge the work of colleagues in these areas (3-6).

STEP ONE: IDENTIFYING POTENTIAL OUTCOMES

We performed a systematic review of randomised trials evaluating therapeutic interventions for treatment of endometriosis (384). We have extracted all outcomes and outcome measures reported within the trial reports. Working with patient and public representatives we have developed lay definitions for these outcomes. The outcomes will be arranged into four domains: harm, pain, quality of life, and subfertility which, following the steering group's agreement, will be entered into a modified Delphi method.

STEP TWO: DETERMINING CORE OUTCOMES

The core outcomes will be determined using a modified Delphi method. The method consists of a series of controlled rounds, where repeated surveys are administered (602). The modified Delphi method facilitates repeated reflection and rescoring. This promotes whole and individual stakeholder group convergence upon a consensus of "core" outcomes and has advantages over less structured consensus methods. An online modified Delphi method allows for scoring without the influence of dominant individuals or junior participants feeling obliged to agree with more senior members. Web based Delphi surveys facilitate international participation and are considered feasible, efficient and acceptable to the user (602,603). The modified Delphi method will be delivered within a web based software hosted, designed and delivered by the University of Liverpool.

All key stakeholders will be invited to participate including gynaecologists managing pain or subfertility associated with endometriosis, family physicians, researchers, and patients. There are no clear recommendations for calculating the required sample size, but based upon previous studies we will aim to include 30 participants from each

stakeholder group. We will recruit at least 36 participants for each stakeholder group anticipating an attrition rate of 20% (9).

10.4.4 ROUND ONE

Participants will be asked to register online, provide demographic details, and commit to all three rounds. They will be allocated a unique identifier which will anonymise their responses. Outcomes will be listed in four domains. Outcomes within each domain will be listed randomly to avoid survey fatigue from perceived repetition. Participants will be asked to score individual outcomes using a seven point Likert Scale anchored between one [not important] to seven [critical]. This scale was created by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group and it has been widely adopted by core outcome set developers (604). During the first round, participants will be invited to suggest additional outcomes. The round will close following a four-week window.

For each outcome, the median and interquartile range of scores will be calculated and summarised graphically for the whole and individual stakeholder group responses using GraphPad Prism (GraphPad, USA). Additional outcomes listed by participants will be reviewed by the outcome committee and, if novel, listed in round two.

10.4.5 ROUND TWO

Participants will be presented with whole group and individual stakeholder group response and asked to reflect on the similarities and differences observed before

proceeding to score each outcome again. The round will close following a four-week window.

For each outcome the median and interquartile range of scores will be summarised graphically by whole and individual stakeholder group response. A standardised definition of this round's results will enable individual outcomes to be classified:
[1] Consensus in (classify as a core outcome): Over 70% of participants in each stakeholder group score this outcome domain 'critical' AND less than 15% of participants in each stakeholder group score outcome domain 'not important'.
[2] Consensus out (do not classify as a core outcome): Over 70% of participants in each stakeholder group score outcome domain 'not important' AND less than 15% of participants in each stakeholder group score outcome domain 'critical'.
[3] No consensus (do not classify as a core outcome): Anything else (602).

If ten or more outcomes have been classified as consensus 'core' outcomes the process will conclude. If less than ten outcomes have been classified as consensus 'core' outcomes a further round will be considered by the steering group.

10.4.6 STEP THREE – STAKEHOLDER CONSULTATION

This final phase will involve a face-to-face meeting with key stakeholders. The meeting will include a range of views from participants that will be purposively sampled from those who have completed all rounds of the Delphi study. The objective of the consensus meeting is to discuss outcomes where there was disagreement in the Delphi study and validate a list of final "core" outcomes. A half-day meeting is planned where the results from each round of the Delphi survey will be presented. To ensure unbiased consensus formation amongst a group of varied participants, the steering committee will ensure that the meeting is informal, inclusive, participatory and values all opinions (603).

To promote wide dissemination, we will invite editors from key journals, for example American Journal of Obstetrics and Gynecology, and funders of endometriosis research.

10.4.7 STEP FOUR – MEASURING CORE-OUTCOMES

Once core outcomes are agreed upon it will be important to determine how the outcomes should be measured. A framework comprising of truth, discrimination, and feasibility exists to assess the quality of potential instruments (605). High quality outcome measures will be associated with each core outcome. The study will not advocate the use of a single outcome measure if several high quality outcome measures are identified for a single outcome. If no high quality outcome instruments exist for a core outcome this will be acknowledged.

10.4.8 IMPACT

Implementing and disseminating a core outcome set for endometriosis in future clinical studies, systematic reviews, and clinical guidelines could make a profound contribution to advancing the reach and relevance of research to inform clinical practice, enhance patient care, and improve patient outcomes.

The selection of appropriate outcomes and outcome measures in future clinical trials is critical. The development of a core outcome set ensures consensus outcomes important to all stakeholders, including patients, are routinely collected and reported. The Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) statement recommends the use of core outcome sets where they exist (606). An endorsement by

national and international funders, including National Institutes of Health, will facilitate [and fund] the collection and reporting of core outcomes.

The Core Outcomes in Women's Health (CROWN) initiative, supported by 78 specialty journals has resolved to implement core outcome sets. Participating journals will require authors to report the results for core outcomes and offer conclusions based on these outcomes rather than non-core or surrogate outcomes (382).

The production of high quantity and quality comparable data to be summarised within systematic reviews to inform clinical practice guidelines would be an important step forward for guideline developers. The National Institute of Clinical Excellence encourages the use of core outcomes sets where available when selecting outcomes during evidence scoping and synthesis. A core outcome set for endometriosis could directly influence national and international clinical practice.

10.5 CONCLUSION

The development of a core outcome set in endometriosis will enable the collection and reporting of a minimum data set important to all stakeholders, including patients. Harmonising outcome collection and reporting for future clinical trials, systematic reviews, and clinical guidelines will make a profound and important contribution to patient care.

This chapter was based on the following peer reviewed publication:

Hirsch M, Duffy JM, Barker C, Hummelshoj L, Johnson NP, Mol B, Khan KS, Farquhar C. Protocol for developing, disseminating and implementing a core outcome set for endometriosis. BMJ Open. 2016 Dec 21;6(12):e013998

APPENDIX

Appendix 1. Contribution to each chapter

- **Chapter 1** – I wrote this chapter entirely
- **Chapter 2** – I conceived the idea for the study, performed searches, selected studies, extracted data, performed quality assessment of studies, created tables, created figures, and drafted the manuscript.
- **Chapter 3** – I conceived the idea for the study, recruited patients, analysed data, created tables, created figures, and drafted the manuscript.
- **Chapter 4** - I conceived the idea for the study, performed searches, selected studies, extracted data, performed quality assessment of studies, created tables, created figures, and drafted the manuscript.
- **Chapter 5** - I conceived the idea for the study, performed searches, selected websites, extracted data, performed quality assessment of websites, created tables, created figures, and drafted the manuscript.
- **Chapter 6** - I conceived the idea for the study, performed searches, selected guidelines, extracted data, performed quality assessment of guidelines, created tables, created figures, and drafted the manuscript.
- **Chapter 7** – I contributed to the study design, performed searches, selected studies, created tables, contributed to drafting original manuscript and this updated version.
- **Chapter 8** - I refined the study, performed searches, selected studies, extracted data, performed quality assessment of studies, created tables, created figures, and drafted the manuscript.

- **Chapter 9** – I conceived the idea for the study, performed searches, selected studies, extracted data, analysed data, performed quality assessment of studies, created tables, created figures, and drafted the manuscript.
- **Chapter 10** - I conceived the idea for the protocol and drafted the manuscript.

Appendix 2: Summary of ESHRE Guidelines for Accuracy Assessment

1. The GDG recommends that clinicians should consider the diagnosis of endometriosis in the presence of gynecological symptoms such as: dysmenorrhea, non-cyclical pelvic pain, deep dyspareunia, infertility, fatigue in the presence of any of the above.

2. The GDG recommends that clinicians confirm a positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis, even though negative histology does not exclude it.

3. Clinicians are recommended to perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma.

4. Clinicians are recommended not to use immunological biomarkers, including CA-125, in plasma, urine or serum to diagnose endometriosis.

5. The GDG recommends clinicians to counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives or progestagens.

6. Clinicians are recommended to prescribe hormonal treatment [hormonal contraceptives (level B), progestagens (level A), anti-progestagens (level A), or GnRH agonists (level A)] as one of the options, as it reduces endometriosis-associated pain.

7. When endometriosis is identified at laparoscopy, clinicians are recommended to surgically treat endometriosis, as this is effective for reducing endometriosis-

associated pain i.e. ‘see and treat’.

8. When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation, as cystectomy reduces endometriosis-associated pain.

9. The GDG recommends that clinicians refer women with suspected or diagnosed deep endometriosis to a centre of expertise that offers all available treatments in a multidisciplinary context.

10. In infertile women with AFS/ASRM stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates.

11. In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates.

12. The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.

13. Clinicians can prescribe GnRH agonists for a period of 3 to 6 months prior to treatment with assisted reproductive technologies to improve clinical pregnancy rates in infertile women with endometriosis.

14. In infertile women with endometriosis, clinicians may offer treatment with assisted reproductive technologies after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for IVF/ICSI.

15. The GDG recommends that clinicians inform women with endometriosis requesting information on their risk of developing cancer that 1) there is no evidence that endometriosis causes cancer, 2) there is no increase in overall incidence of cancer in women with endometriosis, and 3) some cancers (ovarian cancer and non-Hodgkin's lymphoma) are slightly more common in women with endometriosis.

Appendix 3. Summarised guideline recommendations for the diagnosis of endometriosis.

ACOG (2010)	**ACCEPT (2012)**	**CNGOF (2006)**	**ESHRE (2014)**	**NGG (2014)**	**SOGC (2010)**	**WES (2013)**
Mild to moderate endometriosis						
Symptoms	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**
No validated instrument	No recommendations	No recommendations	No validated instrument	No recommendations	No validated instrument	No recommendations
1 non-RCT			1 non-RCT		No reference	
Examination	**Examination**	**Examination**	**Examination**	**Examination**	**Examination**	**Examination**
No recommendations	No recommendations	Pelvic examination	Pelvic examination	No recommendations	Pelvic examination	No recommendations
		No reference	Expert opinion		No reference	
		Rectal examination	Rectal examination		Rectal examination	
		No reference	Expert opinion		No reference	
Imaging	**Imaging**	**Imaging**	**Imaging**	**Imaging**	**Imaging**	**Imaging**
No recommendations	No recommendations	Urinary tract imaging recommended	No recommendations	Transvaginal ultrasound	Transvaginal ultrasound	No recommendations
		No reference		Not recommended	recommended	

				1 systematic review (17 non-RCTs)	No reference	
		MRI not recommended No reference		MRI Not recommended No reference		
Biomarkers <u>Not recommended</u> 3 non-RCTs	**Biomarkers** No recommendations	**Biomarkers** <u>Not recommended</u> No reference	**Biomarkers** <u>Not recommended</u> 3 systematic reviews (266 non-RCTs)	**Biomarkers** <u>Not recommended</u> 1 systematic review (23 non-RCTs)	**Biomarkers** <u>Not recommended</u> 1 systematic review (23 non-RCTs)	**Biomarkers** No recommendations
Diagnostic laparoscopy <u>Histopathology</u> No reference	**Diagnostic laparoscopy** No recommendations	**Diagnostic laparoscopy** <u>Histopathology</u> No reference	**Diagnostic laparoscopy** <u>Histopathology</u> Expert opinion	**Diagnostic laparoscopy** <u>Histopathology</u> 2 systematic reviews (10 RCTs) 1 RCT 1 case series	**Diagnostic laparoscopy** <u>Histopathology</u> No reference	**Diagnostic laparosco** No recommendations
Severe endometriosis						
Symptoms	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**

No validated diagnostic instrument 4 non-RCTs 1 literature review	No recommendations	No recommendations	No recommendations	No recommendations	No validated instrument No reference	No recommendations
Examination No recommendations	**Examination** No recommendations	**Examination** Pelvic No reference	**Examination** Clinical examination 1 non-RCT	**Examination** Pelvic No reference Proctosigmoidoscopy No reference	**Examination** Pelvic No reference Rectal No reference	**Examination** No recommendations
Imaging Transvaginal ultrasound 4 non-RCTs MRI 2 non-RCTs Cystoscopy with biopsy No reference	**Imaging** No recommendations	**Imaging** MRI No reference	**Imaging** Transvaginal ultrasound 1 systematic review 10 non-RCTs Transrectal sonography Expert opinion MRI Expert opinion	**Imaging** Transvaginal ultrasound 1 Systematic Review (10 non-RCTs) 2 non-RCTs Transrectal sonography 1 non-RCT MRI 1non-RCT	**Imaging** Transrectal sonography No reference MRI No reference Cystoscopy No reference	**Imaging** No recommendations

Barium Enema 1 non-RCT			Barium enema Expert opinion Three dimensial ultrasound not recommended 1 non-RCT	Barium enema No reference Cystoscopy No reference	Colonoscopy No reference	
Biomarkers No recommendations	**Biomarkers** No recommendations	**Biomarkers** No recommendations	**Biomarkers** No recommendations	**Biomarkers** No recommendations	**Biomarkers** Not recommended 1 systematic review (23 non-RCTs)	**Biomarkers** No recommendations
Diagnostic laparoscopy No recommendations	**Diagnostic laparoscopy** No recommendations	**Diagnostic laparoscopy** No recommendations	**Diagnostic laparoscopy** Histopathology No reference	**Diagnostic laparoscopy** No recommendations	**Diagnostic laparoscopy** No recommendations	**Diagnostic laparosco** No recommendations
Endometrioma						
Symptoms No recommendations	**Symptoms** No recommendations	**Symptoms** No recommendations	**Symptoms** No recommendations	**Symptoms** No recommendations	**Symptoms** No recommendations	**Symptoms** No recommendations

Examination

No recommendations

Imaging

No recommendations

Biomarkers

No recommendations

Diagnostic laparoscopy

No recommendations

Examination

No recommendations

Imaging

No recommendations

Biomarkers

No recommendations

Diagnostic laparoscopy

No recommendations

Examination

Pelvic

No reference

Imaging

Transvaginal ultrasound

No reference

MRI

Not recommended

No reference

Biomarkers

No recommendations

Diagnostic laparoscopy

No recommendations

Examination

Pelvic

5 non-RCTs

Imaging

Transvaginal ultrasound

1 systematic review

7 non-RCTs

Biomarkers

No recommendations

Diagnostic laparoscopy

Histopathology

Examination

Pelvic

No reference

Imaging

Transvaginal ultrasound

1 non-RCT

Biomarkers

Cancer anitgen-125

2 non-RCTs

Diagnostic laparoscopy

Histopathology

Examination

Pelvic

No reference

Imaging

Transvaginal ultrasound

No reference

Biomarkers

Cancer anitgen-125

1 guideline

1 systematic review

Diagnostic laparoscopy

Histopathology

Examination

No recommendations

Imaging

No recommendations

Biomarkers

No recommendations

Diagnostic laparosco

No recommendations

			Expert opinion	No reference	No reference	
Malignancy						
Symptoms	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**	**Symptoms**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Examination	**Examination**	**Examination**	**Examination**	**Examination**	**Examination**	**Examination**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Imaging	**Imaging**	**Imaging**	**Imaging**	**Imaging**	**Imaging**	**Imaging**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Biomarkers	**Biomarkers**	**Biomarkers**	**Biomarkers**	**Biomarkers**	**Biomarkers**	**Biomarkers**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	Cancer Antigen-125 1 guideline	No recommendations
Diagnostic laparoscopy	**Diagnostic laparoscopy**	**Diagnostic laparoscopy**	**Diagnostic laparoscopy**	**Diagnostic laparoscopy**	**Diagnostic laparoscopy**	**Diagnostic laparosco**
No recommendations	No recommendations	No recommendations	Histopathology Expert opinion	No recommendations	Histopathology No reference	No recommendations
Extra-pelvic endometriosis						

Symptoms

No recommendations

Examination

No recommendations

Imaging

No recommendations

Symptoms

No recommendations

Examination

No recommendations

Imaging

No recommendations

Symptoms

No recommendations

Examination

No recommendations

Imaging

Adenomyosis

Ultrasound

MRI

No reference

Pulmonary endometriosis

Computed tomography

No reference

MRI

No reference

Bronchoscopy

No reference

Symptoms

No recommendations

Examination

No recommendations

Imaging

No recommendations

Symptoms

No recommendations

Examination

No recommendations

Imaging

Adenomyosis

Transvaginal ultrasound

2 systematic reviews

(2 RCTs)

2 non-RCTs

Symptoms

No recommendations

Examination

No recommendations

Imaging

No recommendations

Symptoms

No recommendations

Examination

No recommendations

Imaging

No recommendations

		Pleural endometriosis Thoracoscopy Not recommended No reference				
Biomarkers No recommendations	**Biomarkers** No recommendations	**Biomarkers** No recommendations	**Biomarkers** No recommendations	**Biomarkers** Not recommended	**Biomarkers** No recommendations	**Biomarkers** No recommendations
Diagnostic laparoscopy No recommendations	**Diagnostic laparoscopy** No recommendations	**Diagnostic laparoscopy** Adenomyosis Histopathology at hysterectomy No reference	**Diagnostic laparoscopy** No recommendations	**Diagnostic laparoscopy** Adenomyosis Histopathology at hysterectomy No reference	**Diagnostic laparoscopy** No recommendations	**Diagnostic laparosco** No recommendations

Abbreviations: RCT: Randomised controlled trial.

Appendix 4. Summarised guideline recommendations for the medical and surgical treatment of endometriosis associated pain.

ACOG (2010)	ACCEPT (2012)	CNGOF (2006)	ESHRE (2014)	NGG (2014)	SOGC (2010)	WES (2013)
Medical management of pain associated with mild to moderate endometriosis						
Empirical	**Empirical**	**Empirical**	**Empirical**	**Empirical**	**Empirical**	**Empirical**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Analgesics	**Analgesics**	**Analgesics**	**Analgesics**	**Analgesics**	**Analgesics**	**Analgesics**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Hormonal Treatments	**Hormonal Treatments**	**Hormonal Treatments**	**Hormonal Treatments**	**Hormonal Treatments**	**Hormonal Treatments**	**Hormonal Treatments**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Medical management of pain associated with severe endometriosis						
Empirical	**Empirical**	**Empirical**	**Empirical**	**Empirical**	**Empirical**	**Empirical**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations

Analgesics No recommendations	**Analgesics** No recommendations	**Analgesics** No recommendations	**Analgesics** No recommendations	**Analgesics** No recommendations	**Analgesics** No recommendations	**Analgesics** No recommendations
Hormonal treatments No recommendations	**Hormonal treatments** No recommendations	**Hormonal treatments** No recommendations	**Hormonal treatments** Aromatase inhibitors 2 systematic reviews (5 RCTs, 6 non-RCTs, 7 case reports/series)	**Hormonal treatments** Progestagens No reference monophasic continuous combined oral contraceptive No reference Gonadotropin releasing hormone analogue with add-back HT No reference Levonorgestrel-releasing IUS 1 non-RCT	**Hormonal treatments** No recommendations	**Hormonal treatments** No recommendations
Medical management of endometriosis associated pain						
Empirical treatment 1st line	**Empirical treatment** No recommendations	**Empirical treatment** No recommendations	**Empirical treatment** Nonsteroidal anti-inflammatory drugs	**Empirical treatment** No recommendations	**Empirical treatment** No recommendations	**Empirical treatment** 1st line: Nonsteroidal anti-

Nonsteroidal anti-inflammatory drugs

1 Cochrane review (1 RCT)

Combined oral contraceptive pill

1 Cochrane review (1 RCT)

2nd line

Extended-cycle pills

1 non-RCT

3rd line

Gonadotropin releasing hormone analogues

1 RCT

Expert opinion

Combined oral contraceptive pill

Expert opinion

Progestagens

Expert opinion

inflammatory drugs

1 Cochrane review (1 RCT)

Paracetamol

Expert opnion

Opioids

Expert opinion

Combined oral contraceptive pill

1 Cochrane review (1 RCT)

1 RCT

2 non-RCT

Medroxyprogesterone acetate

2 RCT

Progestagens

anti-progestagens

1 Cochrane review

(13 RCTs)

						Dienogest 6 RCTs 2 non-RCTs 2nd line: <u>Gonadotropin releasing hormone analogues with add-back HT</u> 1 Cochrane review (41 RCTs) Levonorgestrel-releasing IUS 1 Cochrane review (1 RCT)
Analgesics No recommendations	**Analgesics** No recommendations	**Analgesics** Not reported	**Analgesics** Nonsteroidal anti-inflammatory drugs or other analgesics Expert opinion	**Analgesics** Nonsteroidal anti-inflammatory drugs No evidence for use No reference	**Analgesics** Nonsteroidal anti-inflammatory drugs or opioids No reference	**Analgesics** Nonsteroidal anti-inflammatory drugs 1 Cochrane review (1 RCT)
Hormonal treatments <u>Combined oral contraceptive pill</u>	**Hormonal treatments** No recommendations	**Hormonal treatments** <u>Contraceptives</u>	**Hormonal treatments** <u>Combined oral contraceptive pill</u> 1 RCT	**Hormonal treatments** <u>Combined oral contraceptive pill</u>	**Hormonal treatments** 1st line:	**Hormonal treatments** 1st & 2nd line as above

2 Cochrane reviews (2 RCTs)

1 RCT

Gonadotropin releasing hormone analogue with add-back HT

1 Cochrane review (41 RCTs)

3 RCTs

Oral progestins

No reference

Subcutaneous

Depot medroxyprogesterone Acetate

2 RCTs

Levonorgestrel-releasing IUS

3 RCTs

1 non-RCT

Danazol

No reference

No reference

Combined oral contraceptive pill

No reference

Progestins

No reference

Gonadotropin releasing hormone analogue with add-back HT

No reference

Danazol

No reference

Continuous combined oral contraceptive pill

1 non-RCT

Vaginal contraceptive ring or transdermal (oestrogen/progestin) patch

1non-RCT

Progestagens and anti-progestagens

1 Cochrane review (13 RCTs)

Levonorgestrel-releasing IUS

3 RCTs

Gonadotropin releasing hormone analogue with add-back HT

1 Cochrane review (41 RCTs)

4 RCTs

1 RCT

Dienogest

2 RCTs

Gonadotropin releasing hormone analogue with add-back HT

1 Cochrane review (41 RCTs)

1 RCT

Combined oral contraceptive pill

2 RCTs

2 non-RCTs

Oral, intramuscular or subcutaneous progestin

Oral:

Norethindrone Acetate

1 non-RCT

Dienogest

4 RCTs

Intramuscular:

Depot medroxyprogesterone acetate

No reference

Subcutaneous:

Depot medroxyprogesterone acetate

2 RCTs

3rd line: danazol

1 Cochrane review (5 RCTs)

Aromatase inhibitors with progestin or Combined oral contraceptive pill

Not recommended

1 systematic review (1 RCT)

1 non-RCT

7 case reports/series

2nd line:

<u>Gonadotropin releasing hormone analogue with add-back HT</u>

5 non-RCTs

Levonorgestrel-releasing IUS

1 RCT

2 non-RCTs

3rd line:

Danazol

1 Cochrane review (5 RCTs)

1 non-RCT

Aromatase inhibitors

Not recommended

2 non-RCTs

Extrapelvic endometriosis

1st line: Gonadotropin releasing hormone analogue

Extrapelvic endometriosis

No recommendations

Extrapelvic endometriosis

Adenomyoisis –

Extrapelvic endometriosis

Consider medical treatment

1 case series

Extrapelvic endometriosis

Adenomyosis -

Extrapelvic endometriosis

No recommendations

Extrapelvic endometriosis

No recommendations

3 case reports		Antigonadotopic progestins No reference Gonadotropin releasing hormone analogue No reference Levonorgestrel-releasing IUS No reference	2 literature reviews	Combined oral contraceptive pill 1 non-RCT Progestogens 1 RCT Levonorgestrel-releasing IUS 1 non-RCT		
Post-menopausal women No recommendations	**Post-menopausal women** No recommendations	**Post-menopausal women** No recommendations	**Post-menopausal women:** After hysterectomy, avoid unopposed oestrogen treatment. Expert opinion After surgical menopause, treat with add-back HT to the age of natural menopause. Expert opinion	**Post-menopausal women** No recommendations	**Post-menopausal women** No recommendations	**Post-menopausal women** No recommendations
Surgical Management of pain associated with mild to moderate endometriosis						
General Conservative surgery	**General**	**General** No recommendations	**General** No recommendations	**General** No recommendations	**General** No recommendations	**General** No recommendations

1 RCT	No recommendations					
Approach	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Technique	**Technique**	**Technique**	**Technique**	**Technique**	**Technique**	**Technique**
No recommendations	No recommendations	No recommendations	Ablation or excision 2 RCTs	No recommendations	Ablation or excision 1 RCT	No recommendations
Surgical management of pain associated with endometrioma						
General	**General**	**General**	**General**	**General**	**General**	**General**
Cyst >3cm 1 Guideline	No recommendations	No recommendations	No recommendations	No recommendations	Size >3cm: excision Size <3 cm: drainage and coagulation No reference	No recommendations
Approach	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**

Laparoscopic excision 1 RCT	No recommendations	Laparotomy No reference	No recommendations	Laparoscopy 1 Case series	No recommendations	No recommendations
Technique Cystectomy 1 Cochrane review (2 RCTs)	**Technique** Not reported	**Technique** No recommendations	**Technique** Cystectomy 1 Cochrane review (3 RCTs) Cystectomy > CO2 laser vaporisation 1 RCT	**Technique** Cystectomy 1 RCT 1 non RCT	**Technique** Cystectomy 1 Cochrane review (2 RCTs)	**Technique** Cystectomy 1 Cochrane review (4 RCTs)
Extrapelvic endometriosis	**Extrapelvic endometriosis**	**Extrapelvic endometriosis**	**Extrapelvic endometriosis**	**Extrapelvic endometriosis** Appendix: Appendectomy No reference Bladder: Excision and closure No reference	**Extrapelvic endometriosis**	**Extrapelvic endometriosis**

				Abdominal wall / perineal: Excision 5 non-RCT		
Surgical management of pain associated with severe endometriosis						
General	**General**	**General**	**General**	**General**	**General**	**General**
Conservative surgery 1 RCT	No recommendations	No recommendations	Surgical removal 2 systematic reviews (83 non-RCTs)	Pre-menopausal age Hysterectomy with combined HT No reference Post-menopausal age Hysterectomy with combined HT or tibolone 1 literature review 1 consensus statement	Surgical removal 1 non-RCT 1 case series Bowel resection 1 non-RCT Multidisciplinary approach at expert center No reference	No recommendations

Approach

No recommendations

Approach

No recommendations

Approach

Laparoscopy

No reference

Approach

Expert centers

Expert opinion

Approach

Vaginal

No reference

Laparoscopic

No reference

Laparotomy

No reference

Approach

Laparoscopy

National guideline

Approach

No recommendations

Technique

No recommendations

Technique

No recommendations

Technique

Laparoscopic excision

No reference

Bladder:

Partial cystectomy

No reference

Transurethral resection

Not recommended

No reference

Technique

Excisional surgery

1 systematic review (34 non-RCTs)

Technique

Resection, leaving a free margin on all sides

1 systematic review (5 non-RCTs)

Technique

No recommendations

Technique

Excisional surgery

Expert opinion

Hysterectomy

1 non-RCT

Surgical management of endometriosis associated pain						
General	**General**	**General**	**General**	**General**	**General**	**General**
No recommendations	No recommendations	No recommendations	Surgery 1 Cochrane review (5 RCTs)	No recommendations	Surgery 2 RCTs 1 Cohort study Surgery to follow failed medical treatment No reference	Laparoscopic surgery 1 Cochrane review (5 RCTs)
Approach	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**
No recommendations	No recommendations	No recommendations	Laparotomy and laparoscopy No reference	Laparoscopy 1 Cochrane review (5 RCTs)	Laparoscopy 1 non-RCT	Laparoscopy No reference Expert centers Expert opinion
Technique	**Technique**	**Technique**	**Technique**	**Technique**	**Technique**	**Technique**

Hysterectomy with ovarian conservation 1 non-RCT	No recommendations	Hysterectomy with ovarian conservation Not recommended No reference	Ablation or excision 2 RCTs	Methods available (coagulation, vaporisation, excision) are unclear in equivalence 1 RCT	Hysterectomy with ovarian conservation 1 non-RCT	Excision Expert opinion
Hysterectomy with bilateral salpingo-oophorectomy No reference		Hysterectomy with bilateral salpingo-oopherectomy No reference	Hysterectomy and bilateral salpingo-oophorectomy Expert opinion		Conservative surgery No reference	
LUNA Not recommended 1 Cochrane review (6 RCTs) 1 RCT		LUNA Not recommended No reference	LUNA Not recommended 1 Cochrane review (6 RCTs)	LUNA Not recommended 1 RCT	LUNA Not recommended 1 RCT	LUNA Not recommended 1 Cochrane review (5 RCTs)
PSN 1 RCT		PSN Insufficient data No reference	PSN 1 Cochrane review (3 RCTs)		PSN 3 RCTs	PSN Not recommended 1 Cochrane review (4 RCTs)
		Adhesiolysis Insufficient data				

No reference

Adjuvant therapy for the surgical management of endometriosis associated pain						
Preoperative Not recommended 1 non-RCT	**Preoperative** No recommendations	**Preoperative** Not recommended No reference	**Preoperative** Not recommended 1 Cochrane review (16 RCTs)	**Preoperative** **(Endometrioma)** Gonadotropin releasing hormone analogue 1 non-RCT 1 case series **Preoperative** **Severe endometriosis** Gonadotropin releasing hormone analogue Not recommended 1 Cochrane review (16 RCTs) 1 RCT **Preoperative** **Extrapelvic Endometriosis:** **Adenomyosis** - Gonadotropin releasing hormone analogue	**Preoperative** No recommendations	**Preoperative** No recommendations

2 case reports

1 literature review

Perioperative

Not recommended

1 Cochrane review (11 RCTs)

Perioperative

No recommendations

Perioperative

No recommendations

Perioperative

No recommendations

Perioperative

No recommendations

Perioperative

No recommendations

Perioperative

No recommendations

Postoperative

Combined oral contraceptive pill reduces endometrioma recurrence

1 RCT

1 Systematic review (4 RCTs, 3 non-RCTs)

Gonadotropin releasing hormone analogue

1 systematic review (35 RCTs)

1 RCT

Levonorgestrel-releasing IUS

1 Cochrane review (3 RCTs)

Postoperative

No recommendations

Postoperative

Not recommended

No reference

Postoperative

Not routinely recommended

1 Cochrane review (16 RCTs)

Combined oral contraceptive pill

1 systematic review (1 RCT, 1 non-RCT)

Levonorgestrel-releasing IUS

1 Cochrane review (3 RCTs)

1 systematic review (4 RCTs, 3 non-RCTs)

Postoperative

Gonadotropin releasing hormone analogue

Not recommended

1 RCT

Postoperative (Minimal to mild endometriosis)

Levonorgestrel-releasing IUS

1 Cochrane review (3 RCTs)

Postoperative

Severe endometriosis

Gonadotropin releasing hormone analogue

Postoperative

Combined oral contraceptive pill

1 RCT

1 Systematic review (4 RCTs, 3 non-RCTs)

Postoperative

Combined oral contraceptive pill

reduces recurrence

1 RCT

1 RCT				Not recommended 1 Cochrane review (16 RCTs) 1 RCT		
Alternative management of pain associated with endometriosis						
Acupuncture No recommendations	**Acupuncture** No recommendations	**Acupuncture** No recommendations	**Accupuncture** Not recommended Expert opinion	**Acupuncture** No recommendations	**Acupuncture** No recommendations	**Acupuncture** 1 Cochrane review (1 RCT)
TENS No recommendations	**TENS** No recommendations	**TENS** No recommendations	**TENS** Not recommended Expert opinion	**TENS** No recommendations	**TENS** No recommendations	**TENS** 1 Cochrane review (9 RCTs)
Dietary No recommendations	**Dietary** No recommendations	**Dietary** No recommendations	**Dietary** Not recommended Expert opinion	**Dietary** No recommendations	**Dietary** No recommendations	**Dietary** Vitamins 2 RCTs

	Minerals 2 RCTs Salts 2 RCTs Lactic Ferments 2 RCTs Fish Oil 2 RCTS 1 Non-RCT

Abbreviations: CO2: Carbon Dioxide, FDA: Food and Drug Association; HRT: Hormone Replacement Therapy; IUS: IUS; LUNA: Laparoscopic Uterosacral Nerve Ablation; PSN: PSN; RCT: Randomised Controlled Trial.

Appendix 5. Summarised guideline recommendations for the medical and surgical treatment of subfertility associated with endometriosis.

ACOG (2010)	ACCEPT (2012)	CNGOF (2006)	ESHRE (2014)	NGG (2014)	SOGC (2010)	WES (2013)
Artificial reproductive techniques(ART)						
Adjuvant therapy (prior to IVF)	**Adjuvant therapy (prior to IVF)**	**Adjuvant therapy (prior to IVF)**	**Adjuvant therapy (prior to IVF)**	**Adjuvant therapy (prior to IVF)**	**Adjuvant therapy (prior to IVF)**	**Adjuvant therapy (prior to IVF)**
No recommendations	<u>Gonadotropin releasing hormone analogue</u> 1 Cochrane review (3 RCTs) Combined oral contraceptive pill not recommended 1 non-RCT	<u>Gonadotropin releasing hormone analogue</u> No reference *Between cycles:* Progestogens No reference Danazol No reference	<u>Gonadotropin releasing hormone analogue</u> 1 Cochrane review (3 RCTs) *Endometrioma:* Antibiotic prophylaxis at transvaginal oocyte retrival 1 non-RCT	<u>Gonadotropin releasing hormone analogue</u> 1 Cochrane review (3 RCTs)	<u>Gonadotropin releasing hormone analogue</u> 1 Cochrane review (3 RCTs)	<u>Gonadotropin releasing hormone analogue</u> 1 Cochrane review (3 RCTs) Combined oral contraceptive pill not recommended 1 non-RCT
Adjuvant therapy (prior to IUI)	**Adjuvant therapy (prior to IUI)**	**Adjuvant therapy (prior to IUI)**	**Adjuvant therapy (prior to IUI)**	**Adjuvant therapy (prior to IUI)**	**Adjuvant therapy (prior to IUI)**	**Adjuvant therapy (prior to IUI)**

No recommendations

No recommendations

No recommendations

No recommendations

No recommendations

No recommendations

Hormonal treatment

not recommended

1 RCT

ART Technique

No recommendations

ART Technique

Controlled ovarian stimulation

and intrauterine insemination

2 RCTs

ART Technique

First line:

Controlled ovarian stimulation

and intrauterine insemination

No reference

Intrauterine fertilisation

Indication: distorted anatomy

No reference

ART Technique

Controlled ovarian stimulation

and intrauterine insemination

1 RCT

Intrauterine fertilisation

Indication: distorted anatomy

Expert opinion

ART Technique

Intrauterine insemination

2 RCTs

Controlled ovarian stimulation

and oocyte Cryopreservation

1 case report

ART Technique

Controlled ovarian stimulation

and intrauterine insemination

1 RCT

ART Technique

Controlled ovarian stimulation

and intrauterine Insemination

1 systematic review (6 RCTs)

1 RCT

Double insemination at intrauterine insemination

1 non-RCT

Intrauterine fertilisation

1 RCT

Ovulation induction

not recommended

No reference available

Surgical management of infertility associated with mild to moderate endometriosis						
General	**General**	**General**	**General**	**General**	**General**	**General**
Surgery increases spontaneous pregnancy rates. 2 RCTs	Surgery increases spontaneous pregnancy rates 1 Cochrane review (2 RCTs)	Surgery increases spontaneous pregnancy rates No reference Avoid repeat surgery No reference	Surgery increases spontaneous pregnancy rates 1 Cochrane review (2 RCTs) 1 RCT Surgery prior to ART 1 non-RCT	Surgery increases spontaneous pregnancy rates 1 Cochrane review (2 RCTs)	Surgery increases spontaneous pregnancy rates 1 RCT	Surgery increases spontaneous pregnancy rates 1 Cochrane review (2 RCTs)
Approach	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Technique	**Technique**	**Technique**	**Technique**	**Technique**	**Technique**	**Technique**
No recommendations	No recommendations	Laparoscopy excision No reference	Carbon dioxide laser 1 RCT	No recommendations	Excision and ablation equally effective 1 RCT	Not reported

Surgical management of infertility associated with endometrioma						
General Surgery increases spontaneous pregnancy rates. No reference Surgery may damage the ovary and reduce ovarian reserve. No reference	**General** Surgery before IVF Not recommended Cochrane review (3 RCTs)	**General** No recommendations	**General** The decision to proceed with surgery should be considered carefully the woman has had previous ovarian surgery Expert opinion Surgery before IVF Not recommended 2 Cochrane reviews (7 RCTs) 1 non-RCT	**General** No recommendations	**General** Cystectomy >3 cm 1 Cochrane review (2 RCTs)	**General** Surgery before IVF Not recommended No reference
Approach Laparoscopy 1 RCT	**Approach** No recommendations	**Approach** No recommendations	**Approach** No recommendations	**Approach** Laparoscopy 1 non-RCT	**Approach** No recommendations	**Approach** No recommendations
Technique Cystectomy 1 Cochrane Review (2 RCTs)	**Technique** Cystectomy 1 Cochrane review (1 RCT)	**Technique** No recommendations	**Technique** Cystectomy 1 Cochrane review (3 RCTs)	**Technique** Cystectomy 1 Cochrane review (3 RCTs) 1 RCT	**Technique** Cystectomy 1 Cochrane review (2 RCTs)	**Technique** Cystectomy 1 Cochrane review (1 RCTs)

Surgical management of infertility associated with severe endometriosis						
General Benefit unclear 1 non-RCT	**General** Benefit unclear 2 non RCTs	**General** No recommendations	**General** Benefit prior to ART is unclear 2 non-RCTs	**General** No recommendations	**General** Benefits unclear 1 case series	**General** IVF before surgery Expert opinion
Approach No recommendations	**Approach** No recommendations	**Approach** No recommendations	**Approach** Operative laparoscopy 2 non-RCTs	**Approach** No recommendations	**Approach** No recommendations	**Approach** No recommendations
Technique No recommendations	**Technique** No recommendations	**Technique** No recommendations	**Technique** No recommendations	**Technique** No recommendations	**Technique** No recommendations	**Technique** Unclear 6 non-RCTs

Surgical management of infertility associated with endometriosis						
General	**General**	**General**	**General**	**General**	**General**	**General**
IVF > repeat operation, after surgery 1 non-RCT Repetitive ovarian surgery has negative impact on IVF outcomes 1 systematic review (22 non-RCTs)	Primary surgery > repeat surgery 1 systematic review (3 non-RCTs)	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations
Approach	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**	**Approach**
No recommendations	Laparoscopy United Kingdom National Guideline	No recommendations	No recommendations	No recommendations	Laparoscopy 1 case series (1399 cases)	No recommendations
Technique	**Technique**	**Technique**	**Technique**	**Technique**	**Technique**	**Technique**
No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	No recommendations	Excision Expert opinion
Adjuvant therapy for the surgical management of infertility associated with endometriosis (spontaneous conception / Not ART)						

Not Specified	**Not Specified**	**Not Specified**	**Not Specified**	**Not Specified**	**Not Specified**	**Not Specified**
No recommendations	Hormonal treatment Not recommended 1 Cochrane review (23 RCTs) Pentoxifyllline Not recommended 1 Cochrane review (4 RCTs) Hysterosalpingogram with lipidol 1 RCT	No recommendations	Hormonal treatment Not recommended 1 Cochrane review (25 RCTs)	No recommendations	No recommendations	Hormonal treatment Not recommended 1 Cochrane review (23 RCTs) Lipidol hysterosalpingogram 1 RCT
Preoperative	**Preoperative**	**Preoperative**	**Preoperative**	**Preoperative**	**Preoperative**	**Preoperative**
No recommendations	No recommendations	No recommendations	Hormonal treatment Not recommended Expert opinion	Hormonal treatment Not recommended 1 Cochrane review (3 RCTs), 1 case series	Hormonal treatment Not recommended 1 Cochrane review (25 RCTs)	No recommendations

Postoperative No recommendations	**Postoperative** Hormonal treatment Not recommended 1 Cochrane review (8 RCTs) Anti-adhesion treatment Not recommended 1 Cochrane review (3 RCTs)	**Postoperative** Hormonal treatment Not recommended No reference Direct referral to IVF No reference	**Postoperative** Hormonal treatment Not recommended 1 Cochrane review (11 RCTs)	**Postoperative** Gonadotropin releasing hormone analogue Not recommended 1 Cochrane review (24 RCTs) 1 RCT	**Postoperative** Hormonal treatment Not recommended 1 Cochrane review (25 RCTs)	**Postoperative** No recommendations
Alternative management of infertility associated with endometriosis						
Acupuncture No recommendations	**Acupuncture** No recommendations	**Acupuncture** No recommendations	**Accupuncture** Not recommended Expert opinion	**Acupuncture** Not recommended 1 Cochrane review (39 RCTs)	**Acupuncture** No recommendations	**Acupuncture** No recommendations
Dietary No recommendations	**Dietary** No recommendations	**Dietary** No recommendations	**Dietary** Not recommended Expert opinion	**Dietary** No recommendations	**Dietary** No recommendations	**Dietary** No recommendations
TENS	**TENS**	**TENS**	**TENS**	**TENS**	**TENS**	**TENS**

No recommendations	No recommendations	No recommendations	Not recommended Expert opinion	No recommendations	No recommendations	No recommendations

Abbreviations: ART: Artificial Reproductive Techniques, IVF: In Vitro Fertilisation, IUI: Intrauterine Insemination, RCT: Randomised Control Trial, TENS: Transcutaneous Electrical Nerve Stimulation.

Appendix 6. – Peer reviewed publications arising from this thesis with permission to reproduce.

REVIEW

Review of the management of ovarian endometriosis: paradigm shift towards conservative approaches

Dimitrios Psaroudakis, Martin Hirsch, and Colin Davis

Purpose of review
To describe the current consensus regarding the modern management of ovarian endometriosis and summarize the recent evidence that led to a shift in the management recommendations.

Recent findings
The vast majority of the recent studies demonstrate an adverse effect of surgery on ovarian reserve markers, whereas convincing evidence of a benefit of surgery on fertility outcomes is lacking. Current research is focusing on identifying the optimal surgical technique that affords minimal injury to ovarian function. New medical treatment options in the form of aromatase inhibitors are emerging, whereas the evidence for a role of ultrasound-guided drainage and sclerotherapy is scarce and unconvincing.

Summary
Consensus from Europe and the USA is for a conservative approach to the treatment of ovarian endometriosis, with early recourse to assisted reproductive technology for subfertility. Surgery is currently only being advised for severe pain or difficult access to growing follicles and only after careful counselling regarding the potential adverse effect on ovarian reserve. Research has still not identified the optimal technique for treating ovarian endometriosis. Laparoscopic ovarian cystectomy not only offers the lowest risk of recurrence and the highest chance of spontaneous pregnancy rate, but also risks significant injury to ovarian function. Medical treatment offers temporary symptom relief but does not improve the fertility outcomes, and the role of ultrasound-guided drainage remains to be established.

Keywords
artificial reproduction techniques, endometrioma, laparoscopy, ovarian endometriosis, ovarian reserve

INTRODUCTION

Endometriosis is a common condition that affects up to 10% of women in their reproductive years, yet its cause is still relatively poorly understood. It is known to have three common manifestations; ovarian endometriosis, peritoneal endometriosis and deep infiltrating endometriosis [1]. Ovarian endometriomata are special types of ovarian cysts found in 17–44% of women with endometriosis [2], of which between 2 and 50% can be asymptomatic [3].

The manifestation of this enigmatic disease is often pelvic pain and subfertility; its prevalence is up to 50% in women with these two presentations [4]. The mechanisms responsible for increased rates of subfertility are unclear. The prevalent theories of endometriosis-mediated subfertility not only include impaired tubal function as a result of adhesions from pelvic endometriosis, but also an adverse effect on ovulation, oocyte quality and overall ovarian reserve mediated through pressure atrophy, or an adverse effect on the vascularization of normal ovarian cortex from expanding ovarian endometriomata, and through an inflammatory reaction to ovarian endometriomata [5].

Recent research has suggested that surgical treatment of ovarian endometriomata can also have an adverse effect on the ovarian reserve [6**,7**]. This led to controversy over the optimal surgical technique for the treatment of ovarian endometriomata, and to a gradual shift of opinion towards a more

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KEY POINTS

- Surgical treatment of ovarian endometriosis can negatively affect the ovarian reserve.
- Further research is needed to identify the optimal surgical technique for the treatment of ovarian endometriosis.
- Small endometriomas (<3 cm) do not reduce IVF pregnancy rates.
- Current consensus opinion recommends early recourse to IVF for subfertile women with ovarian endometriosis.
- Medical treatment (OCP, progestins, GnRHa and aromatase inhibitors) can help relieve the symptoms and reduce recurrence rates.

conservative approach in the management of ovarian endometriomata, particularly in the context of subfertility.

THE SHIFT OF EXPERT OPINION

In a survey of European gynaecologists, the most common management strategy for ovarian endometriomata was surgery [8]. This practice was based on the widely accepted international guidelines from the European Society of Human Reproduction and Embryology (ESHRE) published in 2005. The guidelines suggested that endometriomata greater than 4 cm in diameter should be treated surgically in order to improve spontaneous pregnancy rates, facilitate access to the ovaries and reduce the risk of infection at transvaginal egg collection, provide a histological diagnosis and possibly improve response to controlled ovarian hyperstimulation (COH) [9]. The recommended surgical technique was laparoscopic cystectomy, using the stripping technique to remove the cyst wall, as this was shown to improve fertility and pain symptoms and have lower recurrence rates compared with drainage and electrocoagulation [10].

The positive effect of cystectomy on spontaneous pregnancy rates has wrongly been extrapolated as a positive effect on assisted reproductive technology (ART) outcomes, leading to the widely accepted practice of surgical treatment for ovarian endometriomata prior to embarking on ART treatment such as in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). However, concerns were raised recently about the potential adverse effect of surgical interventions for ovarian endometriomata prior to ART. Indeed, a recent Cochrane review [11] showed no evidence of benefit on clinical pregnancy rates from surgery for ovarian endometriomata compared to expectant management and warned that cystectomy seemed to reduce the ovarian response during COH even though there was no effect on the number of eggs retrieved. Interestingly, laparoscopic aspiration of ovarian endometriomata was found to increase the ovarian response to COH and increase the number of eggs retrieved compared with expectant management. However, when the pregnancy outcomes of aspiration vs. cystectomy were compared, there was no difference in the clinical pregnancy rate.

Since then, several other studies have raised concerns of a potential adverse effect of surgery for ovarian endometriomata on ovarian reserve and highlighted the lack of convincing evidence of improved pregnancy outcomes in women who had surgery followed by ART [6▪▪,7▪▪,12–15]. This led to the recent recommendations by the American Society for Reproductive Medicine (ASRM) and ESHRE, favouring the conservative management of ovarian endometriomata especially prior to ART treatment [16▪,17▪]. Indeed, the 2013 ESHRE guidelines suggested that surgery should only be considered for ovarian endometriomata greater than 3 cm in diameter and only in order to improve pain symptoms and access to ovarian follicles, and highlighted that there was no convincing evidence that cystectomy prior to ART improves pregnancy rates. Importantly, the authors of the guidelines advised that women undergoing surgery should be counselled about the risk of reduced ovarian reserve and the potential loss of the ovary. It was also noted that the risk of abscess formation after egg collection in the presence of ovarian endometriomata was very low and could be minimized with the use of antibiotic cover; therefore, surgery had no role in preventing infective complications during ART [17▪].

ENDOMETRIOMA AND OVARIAN RESERVE: INHERENT OR IATROGENIC INJURY

The effect of ovarian endometriomata on ovarian reserve has been the subject of much controversy in the recent years. Ovarian reserve can be measured using ultrasonic markers such as antral follicle count (AFC), biochemical markers including anti-Mullerian hormone (AMH) and follicle-stimulating hormone (FSH) levels, histological markers like follicular density and, perhaps most importantly, clinical markers including response to COH and pregnancy rates.

The mere presence of ovarian endometriomata has been associated with a reduced ovarian reserve as evidenced by a 31% reduction in ovulation rate in

the ovaries containing ovarian endometriomata compared with healthy ovaries [18] and lower baseline AMH levels in the presence of ovarian endometriomata [19,20]. Clinical markers of ovarian reserve have also suggested an adverse effect of the presence of ovarian endometriomata on COH [21]. Histological studies have also suggested that ovarian endometriomata have an adverse effect on the ovarian reserve as evidenced by reduced follicular density in ovarian cortex surrounding ovarian endometriomata compared with cortex around other benign cysts [22–24], especially in younger patients (<35 years old) [25]. However, there has been no reduction in the ovarian response to COH when comparing ovaries containing small (<3 cm) endometriomata to unaffected ovaries [26–28], suggesting that the size of ovarian endometriomata is important in determining the effect on ovarian response. It has been shown that small (mean diameter 23 mm) bilateral ovarian endometriomata have a quantitative rather than qualitative effect on ovarian response as evidenced by a reduced growing follicle number but no effect on oocyte quality or clinical pregnancy rates [29].

Overall, there is evidence that ovarian endometriomata can be detrimental to fertility, but this does not always justify their surgical treatment. A meta-analysis in 2009 found no adverse effect of surgical treatment of endometriomata on the outcomes of ART treatment when compared to conservative management [30]. Recent evidence suggests that surgery can in fact compromise ovarian reserve. In extreme cases, a 16.3% rate of premature ovarian failure [31] and a 13% rate of failure to respond to gonadotrophin stimulation [14] have been reported.

Mechanisms of surgical damage include accidental removal of healthy tissue during endometrioma cystectomy and direct damage to ovarian cortex following surgical haemostasis and scar tissue formation.

Earlier reports had shown a reduced ovulation rate following endometrioma surgery [18,32], but a more recent research has focussed on the effect of surgery on the surrogate serum markers, of which AMH has been shown to be the most reliable [33,34]. Two recent meta-analyses [6**,7**] showed strong evidence of sustained reduction in the postoperative AMH levels of up to 40% after ovarian surgery, with the decline being more pronounced in bilateral surgery and in women over 38 years old [35]. Further studies have shown a sustained reduction in AMH levels for at least 6 months after surgery [20,35–38]. This correlates with the bilaterality and severity of endometriosis [39], and with cyst size [40]. Interestingly, two groups have demonstrated a partial recovery in AMH levels up to 65% of preoperative levels 3 months after surgery [41,42]. Mechanisms implicated in this recovery of ovarian function include re-vascularization after surgery, compensation from remaining follicles or an unaffected ovary [5] and rearrangement of follicle cohorts [43].

Histological studies offer an explanation for this partial recovery with healthy ovarian tissue removed in 85–97% of excised endometrioma specimens [25,44,45]. The size of the endometrioma is an important determinant of the amount of healthy tissue removed, with 200 μm of tissue lost per cm increase in cyst diameter [44]. Healthy ovarian tissue is found in the majority of endometrioma cyst wall specimens, even in the hands of experienced surgeons [46]. There is little evidence to suggest that the degree of surgical experience, amongst appropriately trained laparoscopic surgeons, has a significant detrimental effect on postoperative ovarian reserve [47–49].

CURRENT TREATMENT OPTIONS FOR OVARIAN ENDOMETRIOSIS

Given the above concerns of the potential adverse effect of surgical treatment of ovarian endometriomata on ovarian tissue and function, efforts have focussed on identifying the optimal treatment modality for ovarian endometriomata. In this section, we review the evidence for the various treatment options.

Medical therapy

It is now widely accepted that ovulation plays a fundamental role in the pathogenesis of ovarian endometriomata. Consequently, therapies that inhibit ovulation, such as the oral contraceptive pill, progestins, gonadotrophin-releasing hormone agonists (GnRHa) [17*] and aromatase inhibitors [50], have all been shown to decrease the cyst size, improve symptoms and reduce the risk of postsurgical recurrence [51]. However, symptoms tend to recur in the majority of cases upon discontinuing medical treatment. Crucially, medical treatment prior to ART has not been shown to improve the reproductive outcomes and is, therefore, not routinely recommended. The notable exception is treatment with GnRHa for 3–6 months prior to ART, which has been shown to increase the odds of clinical pregnancy by four-fold [52].

Medical therapy has also been used prior to surgical treatment. Prolonged hormonal downregulation has been commonly used in an attempt to decrease the cyst size, reduce bleeding and facilitate surgical removal. However, concerns have been raised that this strategy can induce fibrosis of the cyst capsule and make stripping of the cyst more

difficult, thus risking the loss of healthy ovarian tissue [46,53].

Ultrasound-guided drainage and sclerotherapy

The concerns regarding the effect of surgery on ovarian function together with the surgical risks associated with a surgical approach to treating ovarian endometriomata have led researchers to seek less invasive treatments such as ultrasound scan (USS)-guided drainage, usually combined, with irrigation with a sclerosing agent. Sclerosing agents tried in the past include ethanol [54], tetracycline [55], synthetic interleukin-2 [56] and methotrexate [57]. Unfortunately, results have in general been disappointing with very high recurrence rates (up to 83.3% at 3 months [58]), concerns regarding the risk of abscess formation and missing occult malignancy, and lack of improvement in reproductive outcomes after ART [59–62].

More recently, Wang *et al.* [63] reported a 96% cure rate following USS-guided aspiration and sclerotherapy with 95% ethanol for recurrent endometriomata and Zhu *et al.* [64] demonstrated that repeated aspiration reduced the recurrence rate to 5.4% at months after a mean of 3.1 aspirations with an overall pregnancy rate of 43.4%. Neither group reported any major complications in their patients, but a recent study on an animal model of endometrioma aspiration and ethanol sclerotherapy raised the concern of a reduction in the ovarian reserve following the treatment [65].

Overall, USS-guided endometrioma drainage does not seem to have a role in the current management of the disease as it has a poor efficacy in relieving the symptoms and a high risk of introducing infection and cyst recurrence [64]. It may, however, have a role in facilitating oocyte retrieval in patients who decline or are not fit for surgery to improve access to follicles.

Surgical techniques

Advantages of surgery for ovarian endometriomata other than symptom improvement include obtaining a histological diagnosis of the cyst (there is an ~0.8% risk of occult malignancy [66]), improving monitoring of follicular growth and access to the follicles during ART, and reducing the small risk of pregnancy complications such as spontaneous endometrioma rupture [67–69].

Disadvantages of surgery other than the potential adverse effect on ovarian reserve include the delay in commencing ART, the cost of surgery [70] and the risk of surgical complications [71].

It is known that the wall of an endometrioma contains endometriotic tissue covering 60% of the inner wall surface and the depth of penetration is no more than 1.5 mm [72]. The key of successful surgery, therefore, is to remove the maximum amount of endometriotic tissue, and hence reduce the risk of recurrence, whilst keeping bleeding at a minimum, and hence reducing the need for haemostatic measures that can damage the ovarian reserve.

Surgical techniques that have been described in the literature include laparoscopic drainage and ablation (with various different energy sources), laparoscopic cystectomy (using the stripping technique), combination techniques, the vasopressin technique (aiming for relatively bloodless hydrodissection with diluted vasopressin) and aggressive treatment in the form of oophorectomy (see Table 1) [20,25,35–38,40,42,43,73–92]. In centres in which minimal access surgical expertise is not available, open surgery still has a role [92].

Unfortunately, it is difficult to identify the optimal surgical technique as there is marked heterogeneity in terms of disease severity and surgical technique amongst the reported studies, and a relative scarcity of evidence from high-quality randomized controlled trials (RCTs). Nevertheless, a recent meta-analysis showed that laparoscopic cystectomy has lower recurrence and higher spontaneous pregnancy rates compared with laparoscopic drainage and bipolar ablation, and lower recurrence and similar spontaneous pregnancy rates compared with drainage and laser ablation [93▪▪]. The available data were inadequate for a meta-analysis on the effect of different surgical techniques on ovarian reserve in this study; however, the authors reported consistently better outcomes in terms of postoperative AFC and AMH levels with ablative techniques compared with cystectomy.

Plasma energy coagulation has appeared as an attractive energy modality, as it offers a low depth of tissue penetration (<1.5 mm), thus limiting damage to the healthy ovarian tissue [94]. Evidence from preliminary studies appears promising, with a small beneficial effect on the ovarian reserve markers compared with cystectomy [74] and comparable low recurrence and high pregnancy rates [75]. The clinical relevance of these results remains to be confirmed in large RCTs.

A recent prospective study [81] has suggested that using intracortical ovarian suture to achieve haemostasis following cystectomy can protect future ovarian function. However, the available evidence so far has failed to demonstrate a clear superiority of suturing compared with bipolar coagulation [78–80]. This could be because suturing can also cause ischaemic changes and postoperative

Table 1. Summary of the studies of different surgical techniques for the treatment of OEs and their effect on ovarian reserve

Reference	Type of study	n	Cyst characteristics: Laterality (unilateral/bilateral)	Cyst characteristics: Mean diameter (mm)	Surgical technique	Outcomes
Asker *et al.* [73]	Retrospective, noncomparative	10	Unilateral	≥30	Plasma energy ablation	Surgery causes a small reduction in ovarian volume and AFC
Roman *et al.* [74]	Retrospective, comparative	30	Unilateral	≥30	Plasma energy ablation vs. cystectomy	Larger reduction in ovarian volume & AFC with cystectomy
Roman *et al.* [75]	Retrospective, noncomparative	55	NR	<30	Plasma energy ablation	Recurrence rate 10.6%
						Pregnancy rate 67%
Saeki *et al.* [76]	RCT	15	Unilateral	45–54	Cystectomy, vs. cystectomy and saline injection, vs. cystectomy and vasopressin injection	Less need for coagulation in vasopressin group
Qiang-Zhen *et al.* [77]	RCT	86	Bilateral	40–60	Cystectomy, vs. cystectomy and saline, vs. cystectomy and vasopressin injection	Lower postoperative FSH and less tissue loss in the vasopressin group
Coric *et al.* [78]	RCT	45	Unilateral	40	Laparoscopic cystectomy and suturing, vs. bipolar	Lower AFC in bipolar group
Ferrero *et al.* [79]	RCT	100	Bilateral	70	Laparoscopic cystectomy and suturing, vs. bipolar	No difference in drop in AMH or rise in FSH between groups
Takashima *et al.* [80]	Retrospective, comparative	44	Unilateral	62	Laparoscopic cystectomy and suturing, vs. bipolar	No difference in preoperative and postoperative AFC, AMH, FSH, or pregnancy rates between groups
Uito *et al.* [81]	Prospective	25	Unilateral	47	Laparoscopic cystectomy and suturing	Nonsignificant decrease in AMH after operation
Tsolakidis *et al.* [82]	RCT	20	NR	≥30	Three-stage technique vs. standard cystectomy	Less reduction in AFC and AMH with three-stage technique
Donnez *et al.* [83]	Prospective	52	Unilateral	52	Partial cystectomy and laser vaporization	No difference in ovarian volume or AFC between operated and healthy ovaries
Carmona *et al.* [84]	RCT	90	Both	≥30	Cystectomy vs. laser ablation	Earlier and higher recurrence rate in laser group
Takekayashi *et al.* [85]	Retrospective, comparative	27	Both	20–70	Cystectomy vs. laser ablation	Lower pregnancy rate in laser group
Vlar *et al.* [86]	RCT	48	Bilateral	40–60	Cystectomy vs. bipolar coagulation	Lower AFC, ovarian volume & number of oocytes retrieved in cystectomy group
Ercan *et al.* [87]	Prospective	47	Both	67	Laparoscopic cystectomy	No effect of surgery on AMH
Lee *et al.* [88]	Prospective	27	Unilateral	40–70	Laparoscopic cystectomy vs. oophorectomy	Similar reduction in AMH in both groups
Hwu *et al.* [89]	Retrospective, comparative	1642	Both	NR	Laparoscopic cystectomy	Endometrioma and cystectomy both reduce AMH
Ercan *et al.* [90]	Prospective	36	Unilateral	≥40	Laparoscopic cystectomy	No effect on ovarian volume and AMH at 3 months

Table 1 (Continued)

Reference	Type of study	n	Cyst characteristics: Laterality (unilateral/bilateral)	Cyst characteristics: Mean diameter (mm)	Surgical technique	Outcomes
Kitade *et al.* [25]	Prospective	108	Both	59–77	Laparoscopic cystectomy	More ovarian tissue excised at endometrioma than none endometrioma cystectomy
Suksompong *et al.* [42]	Prospective	43	Both	≥40	Laparoscopic cystectomy	Cystectomy reduces AMH
Celik *et al.* [36]	Prospective	65	Both	≥30	Laparoscopic cystectomy	Cystectomy reduces AMH
Uman *et al.* [37]	Prospective	25	Unilateral	51.5	Laparoscopic cystectomy	Cystectomy reduces AMH
Uncu *et al.* [20]	Prospective	60	Both	>20	Laparoscopic cystectomy	Cystectomy and presence of endometriomata reduce AMH
Tong *et al.* [40]	Retrospective	85	Unilateral	≥10	Laparoscopic cystectomy	Cystectomy reduces AFC
Sugita *et al.* [43]	Prospective	39	Both	>37	Laparoscopic or open cystectomy	Surgery reduces AMH (degree recovery with time)
Kwon *et al.* [38]	Prospective	100	Both	63.3	Laparoscopic cystectomy	Cystectomy reduces AMH
Alborzi [35]	Prospective	193	Both	NR	Laparoscopic cystectomy	Cystectomy decreased AMH and raised FSH
Streuli *et al.* [91]	Prospective cohort	726	Both	NR	Previous endometrioma surgery	Previous endometrioma surgery decreases AMH
Zaitoun *et al.* [92]	RCT	121	Unilateral	NR	Open cystectomy and suture, vs. laparoscopic cystectomy & bipolar	Higher FSH and lower AMH in laparoscopy group

AFC, antral follicle count; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; NR, not reported; OEs, ovarian endometriomata; RCT, randomized controlled trial.

adhesions that can adversely affect ovarian function.

Combined techniques have also shown promising results. Partial cystectomy of 80–90% of the endometrioma wall combined with CO_2 laser vaporization to the ovarian hilum (in which the plane of cleavage is not easily identified) maintained postoperative ovarian volume and AFC, and resulted in a low recurrence rate (2%) and a 41% spontaneous pregnancy rate at a mean follow-up of 8.3 months [83]. Similarly, a three-stage technique of laparoscopic cyst drainage, followed by treatment with GnRHa for 3 months before a repeat laparoscopic laser ablation of the cyst wall, was shown to result in less reduction in AFC and AMH compared with cystectomy in a small RCT [82].

Finally, two recent studies [76,77] have shown promising results using the vasopressin technique, in which a solution of diluted vasopressin was injected in the endometrioma cyst wall prior to cystectomy. Employing this technique, the hydrodissection can help identify the plane of cleavage, whilst the vasoconstrictive effect of vasopressin reduces the need to use other haemostasis control methods and thus helps preserve ovarian function.

Overall, there is a growing consensus that endometriomata should not be routinely removed prior to ART and research is focussing in improving the surgical techniques to best preserve postoperative ovarian function for those patients in whom an operation is deemed necessary.

CONCLUSION

Ovarian endometriosis remains a challenging disease. The role of medical treatment is mostly for temporary symptom relief and recurrence prevention, whereas USS-guided drainage has a very limited, if any, role in the current practice. There is growing evidence that both the physical presence of ovarian endometriomata and the surgery to remove them can further adversely affect the ovarian function, and thus the consensus has now shifted towards a more conservative approach in treatment [16",17",95].

A decision to perform surgery for ovarian endometriomata depends on the severity of symptoms, concern regarding malignancy, access to follicles and desire to preserve fertility, and should be made on a case-by-case basis after fully informed consent;

the risks to ovarian reserve must be discussed. Ideally, surgery should be reserved for symptomatic patients after their family is complete. Repeat surgery is best reserved until fertility is no longer desired.

For patients with subfertility and ovarian endometriomata, we recommend that ovarian reserve and other fertility parameters should be assessed preoperatively and that ART treatment should be the first option, particularly in the presence of a preexisting reduced ovarian reserve or other subfertility factors. This should also be the case for patients with small (<3cm) ovarian endometriomata as these do not seem to affect the ART outcomes.

As far as the ideal surgical technique is concerned, evidence from high-powered comparative RCTs is urgently needed. In the meantime, the key to successful surgery might be to avoid bleeding and the consequent need for haemostasis, as this would further compromise ovarian function. Considerable surgical skill is required to achieve the optimal balance between minimal ovarian damage and incomplete surgery, but what is critical is for both the surgeons and the patients to discuss in detail the benefits and risks involved and reach individualized, often conservative, decisions on treatment rather than aggressive one-fits-all approaches.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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REVIEW

Preoperative assessment and diagnosis of endometriosis: are we any closer?

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Purpose of review
The management of endometriosis has progressed vastly with medical treatments providing a large role in controlling endometriosis symptoms. Despite these advances we still lack an accurate noninvasive test to diagnose endometriosis. This has a large role in the delay to diagnosis, management and progression of the disease amongst a population that is choosing to conceive later.

Recent findings
Endometriosis is now thought to affect 1 in 10 women with patient annual healthcare costs estimated at €9579. The diagnosis of this disease is still delayed by an average of 6–9 years allowing disease and symptom progression. Researchers have assessed a wide variety of noninvasive markers from urinary derivatives to MRI. There has been limited success in producing a highly sensitive and specific preoperative test for endometriosis. Novel markers such as miRNA provide the most encouraging diagnostic accuracy.

Summary
The development of a noninvasive accurate marker for endometriosis is a research target and priority of the European Society of Human Reproduction and Embryology. The current markers in use have moderate sensitivity and sensitivity. The inflammatory basis for the disease underpins many biomarkers but also many other concomitant diseases reducing accuracy and increasing false positive results.

Video abstract
http://links.lww.com/COOG/A26

Keywords
diagnosis, endometriosis, imaging, screening test, serum, urine

INTRODUCTION

Endometriosis is a varied and enigmatic disease. It is histologically characterized by the presence of ectopic endometrial glands and stroma distant to the uterus. Common sites include the pelvic organs and the peritoneum surrounding the uterus [1]. Endometriosis is a chronic benign oestrogen-dependent disease affecting 10% of women during their reproductive years [2]. The prevalence increases to 35–50% amongst women with pelvic pain and or subfertility [3–6]. Endometriosis is often undiagnosed, and average delays from symptom onset to diagnosis are 6–11 years [7–9]. Endometriosis is characterized clinically by noncyclical pelvic pain, dysmenorrhoea, dyspareunia and subfertility [10–13]. The disease has estimated annual costs of €9579 per patient, comprising one-third of the direct healthcare costs with two-thirds attributed to loss of productivity [14].

The disease manifests itself in three distinct visually and pathological forms: superficial peritoneal, ovarian endometrioma and deep infiltrating endometriosis. There is significant heterogeneity between these three disease forms and debate is ongoing whether despite their similar histopathological appearance they are in fact separate processes [15]. The surgical findings are widely classified according to the revised American Fertility Society (rAFS) despite this having very poor correlation with postoperative outcomes, symptomatology and high intrauser variability [16–18].

The development of a screening test for endometriosis relies on several critical properties including high specificity, high sensitivity, reproducibility,

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KEY POINTS

- The development of a diagnostic test in endometriosis has been highlighted a clinical priority.
- MiRNA analysis is a growing area of biomarker development with some of the highest levels of noninvasive diagnostic accuracy.
- Where there is clinical suspicion, preoperative MRI is recommended to exclude deep infiltrating endometriosis (DIE) as this offers high-level diagnostic accuracy for the presence of DIE of the rectum, pouch of Douglas and utero-vesical space.
- The use of recently published ultrasonic signs such as 'the sliding sign' to assess the mobility of pelvic organs has provided high accuracy in a limited number of studies for the detection of deep infiltrating endometriosis. This sign is not routinely assessed in pelvic ultrasonography and may require educational provision before it is accepted into widespread clinical practice.

simplicity and patient acceptability or minimal invasiveness. A marker or test must provide consistent results among a varied geographical and ethnically varied population. This marker or test has not been able to meet these criteria nor has it been validated and as a result this has been highlighted as an endometriosis research priority [19].

CURRENT GUIDANCE

To date, we have been unable to accurately predict the presence of endometriosis with symptom, clinical, blood, urine nor image-based screening tests. The combination of laparoscopy and histopathological confirmation is currently the gold standard for diagnostic confirmation of endometriosis [20**]. Endometriosis has a myriad of macroscopic appearances that can lead to false-negative and false-positive diagnosis via visualization alone [21]. This is more evident in peritoneal endometriosis than ovarian and deep infiltrating endometriosis; nonetheless, the visual diagnosis of endometriosis has been demonstrated to be unreliable [22,23]. The European Society of Human Reproduction and Embryology committee of endometriosis experts set up a guideline development group that stated visually confirmed endometriosis at laparoscopy is of limited value without a biopsy confirming histological presence [20**]. A study supporting this excised 122 visually confirmed endometriosis lesions from 54 patients and found that only 54% of these lesions were histopathologically confirmed endometriosis [24]. This limited diagnostic accuracy of visualization was compounded by a meta-analysis of studies demonstrating close to 50% misdiagnosis in rAFS stage I–II with visualization alone [23]. The combination of poor diagnostic accuracy and poor prognostic capabilities of disease presence and quantity makes for challenging consultations with patients when discussing the management of the disease.

THEORIES OF DEVELOPMENT

The basis and theories behind many diagnostic studies lie in the multitude of theories that underpin the origins and aetiology of endometriosis. Retrograde menstruation was first postulated in 1925 by Sampson [25] and was subsequently shown to occur in over 90% of menstruating women, yet only 6–10% of women develop endometriosis [26]. Further studies looking at women with menstrual outlet obstruction from cervical stenosis, congenital anomalies or imperforate hymen have demonstrated a higher prevalence of the disease [27–30]. Coelomic metaplasia describes a process in which abnormal embryogenesis results in mesothelial cells lining the peritoneal cavity which are prone to metaplasia and transformation into endometrial cells under hormone influence. This has been described with autopsies on female human foetuses from 20 weeks of gestational age demonstrating epithelial cells lining the pelvic peritoneum [31–34]. Immunodeficiency theories postulate that refluxed endometrial cells produce a localized inflammatory response masking the endometrial cells and preventing their removal [33–36]. This reaction augments implantation via angiogenesis and cell proliferation.

Many studies have looked at developing a diagnostic test to accurately predict endometriosis. Inherent difficulties lie not only within the diagnosis of the disease but multiple other variables including menstrual timing, menstrual regularity, hormone use, age, ovarian function and the presence of fibroids and adenomyosis. Inter and intrauser variability of disease classification and staging add to difficulties in conducting a diagnostic surgical trial.

BLOOD MARKERS

The chronic inflammatory nature of endometriosis further challenges the specificity of tests based on mediators of inflammation. The most commonly used biomarker for preoperative assessment is cancer antigen 125 (CA-125). This is a glycoprotein found within the cells lining the female genital tract and is raised in both epithelial ovarian cancer and other gynaecological diseases [37–39]. This was systematically reviewed with a meta-analysis finding

insignificant sensitivities and specificities to justify its use as a predictive marker [38] though serum levels appear to rise with increasing disease severity [40▪▪]. CA-125 along with other glycoproteins has been analysed by research teams in Leuven who have kept a bank of frozen blood samples from patients since 1999. The team were able to demonstrate the accuracy of CA-125 with sensitivity of 78 and 51%, respectively, whereas CA 19–9 performed less consistently with sensitivities and specificities of 55 and 58%, respectively [41]. There are significant data to suggest that CA-125 has a limited role in the assessment and follow-up of endometriosis [42] with VEGF potentially providing a more accurate means of diagnosis with sensitivities and specificities of 93.3 and 96.7%, respectively [43].

Inflammatory markers such as interleukin-8 [44] and high-sensitivity C-reactive protein (hs-CRP) [45▪▪] have been analysed in large trials. The use of C-reactive protein (CRP) in the detection of many inflammatory conditions is widely recognized, yet its use in endometriosis is uncertain. Previous studies have demonstrated hs-CRP as a more useful marker than CRP but without conclusively demonstrating its use as a marker in its own right [46–49]. Thubert *et al.* [45▪▪] examined the significance of hs-CRP in 370 women with histopathological confirmed endometriosis compared with those patients ($n = 464$) who had had negative laparoscopies. Over a trial period of 4 years, the authors demonstrated no significant difference in this marker between the case and control group [45▪▪].

Endometriosis is widely considered an inflammatory process of unclear aetiology. The inflammation pathway is associated with oxidative stress [50] which results in the production of free radicals and reactive oxygen species [50]. When these by-products are not adequately metabolized and removed, they may cause oxidative alteration in proteins, lipids, carbohydrates, nucleic acids and their sequential signalling pathways. This cascade of events that follows oxidative stress requires several key components including thiols and carbonyls that have become the focus of biomarker analysis [51] and have been linked to endometriosis and subfertility [52,53▪]. In the quantitative analysis of serum thiols in 67 cases of histologically confirmed endometriosis compared with 41 controls, quantitative analysis demonstrated significantly lower levels of thiols and carbonyls amongst endometriosis cases compared with controls. Receiver operating curve analysis provided cut-off levels at 396.44 μM and 14.9 μM for thiols and carbonyls, respectively, and sensitivity of 73.1% and specificity of 80.5% for thiols and 94 and 51.2% with carbonyls [54▪]. This finding was contradicted by several studies demonstrating no association between endometriosis and markers of oxidative stress [55,56].

More recent areas of biomarker development have included micro RNAs (miRNAs). These circulating lengths of 19–25 nucleotides have been demonstrated to influence mRNA translation and degradation resulting in a sequential impact on gene and proteomic expression [57–59]. The aberrant expression of miRNA has been linked to chronic diseases including endometriosis [60]. Variation between miRNA levels in eutopic and ectopic endometrium of controls and those patients with endometriosis has led to further analysis of serum miRNA profiles [61–64]. A quantitative analysis of miRNA levels in women with stage III–IV endometriosis demonstrated high levels of accuracy with sensitivities and specificities up to 90% for miRNA-17-5p, miRNA-20a, miRNA-22 [65]. This contrasts to Suryawanshi *et al.* [66] who found differentiation between endometriosis patients and controls with miRNA-16, miRNA-191 and miRNA-195 at sensitivity and specificity of 88 and 60%, respectively. The most promising study yet from Wang *et al.* [67] compared 60 patients with histopathological confirmed endometriosis to 25 patients with a negative laparoscopy. This study found discriminatory sensitivities and specificities of 93.2 and 96% when combining miR-199a, miR-122, miR-542-3p and miR-145. This field of endometriosis research appears to be a growing area of interest.

ENDOMETRIAL MARKERS

The hormonal variation in ovulatory women throughout their menstrual cycle results in endometrial molecular signature change depending on the stage in the cycle. This presents a significant challenge with regard to endometrial-based biomarker development. Although a cycle phase-specific test may be acceptable to optimize sensitivities and specificities, this may not be practical with women having irregular menstrual cycles. This is particularly relevant in studies analysing eutopic mRNA expression [68].

Recent studies have found associations between endometrial nerve fibre density and endometriosis. The association between protein gene product 9.5 in the functional layer of the endometrium and the presence of endometriosis in the pelvis has, like many markers, shown promise [68–74]. This C-terminal hydrolase dissociates ubiquitin peptide bonds and thus regulates proteolysis [75]. The use of this semi-invasive biomarker has sensitivities ranging from 80 to 81% with specificity 92–100% and did not appear to vary by phase of the menstrual cycle

[74,76*]. Protein expression correlated with the presence of endometriosis, whereas the gene expression did not; this discordance between genomic expression and proteomic expression suggests that expression of these proteins is influenced by mechanisms taking place in the posttranscription period [76*].

URINARY MARKERS

Urinary cytokeratin 19 fragments have been analysed with limited reliability. An initial scoping review study found over 130 differentially expressed urinary proteins as potential markers for endometriosis. This small study found cytokeratin 19 (CK19) as the most accurate of urinary protein markers for endometriosis [77]. Little is known about the role of CK19 in endometriosis, but further studies have continued to demonstrate a high specificity (94%) but a low sensitivity (11%) in a population of 98 women with pelvic pain. In the group which had a negative index test (CK19), 56 of the 89 (62%) were found to have histologically confirmed endometriosis compared with two patients from nine who had a false-positive result exposing many women to unnecessary interventions [78*].

A Study of Chinese women undergoing gynaecological investigation examined the role of urinary proteomic expression as a screening tool. The significance of urinary angiogenic markers and cytokines has previously been demonstrated in both systemic and urogenital diseases such as nephrotic syndrome, hypertension and cardiac failure [79–83].

ELISA analysis of creatinine-adjusted urinary vitamin-D binding protein for 57 women with endometriosis compared with control group of 38 women without endometriosis produced a sensitivity of 58% and specificity of 76% [84].

CLINICAL SYMPTOM PREDICTION MODELS

Endometriosis is known for a triad of pain symptoms: dysmenorrhoea, dyspareunia and pelvic pain; however, multiple symptom-based predictive tools have failed to accurately predict endometriosis from those without endometriosis. A detailed pelvic examination has previously been unable to accurately predict the presence of endometriosis as many women have normal findings [85,86]. The ill-defined relationship between clinical stage (rAFS) and symptom severity provides clinicians with further challenges. Several systematic reviews and studies of endometriosis have attempted to develop predictive analysis with a combination of examination, symptoms and ultrasound to add diagnostic accuracy to tools which are individually imprecise [87–89]. Despite the low individual clinical accuracy, pelvic examination remains a crucial component to the preoperative assessment.

IMAGING PREDICTION

Imaging modalities have a major role in the investigation and diagnosis of gynaecological disease. Ultrasound alone provides high sensitivities of up to 97% in stage three or four endometriosis but consistently low sensitivities of 10% in stage one/two endometriosis. This demonstrates an ability for a positive scan result to diagnose the disease but not exclude the disease when it is negative [90].

Ultrasound imaging has a historic use in identifying ovarian endometrioma. The diagnosis of endometrioma with ultrasound has moderate sensitivities but high specificities, using three commonly reported ultrasound signs: ground glass appearance, septations 1–4, papillaries without blood flow. When premenopausal status is added, the sensitivities range from 62 to 73%. The experience and subjective assessment of a senior trained sonographer increases sensitivities to 81% [91,92].

Endometriosis is a disease characterized by inflammation and fibrosis more commonly causing adhesions rather than ovarian endometrioma [93]. Several ultrasound studies have tried to address this as a potential area for noninvasive diagnosis. Adhesions are not well visualized on ultrasound and in the absence of endometriosis or other inflammatory processes, the uterus and ovaries can move freely. However, when endometriosis is coexistent, adhesions commonly form between the ovary and the uterus increasing in frequency and severity with advancing disease preventing this movement [94]. Several studies have looked to assess the diagnostic accuracy of adhesions or pelvic immobility at ultrasound to predict endometriosis presence at surgery [95–97,98**]. The diagnostic accuracies are variable with a potential use in the diagnosis of deep infiltrating disease, pouch of Douglas obliteration [97,98**] and ovarian adhesions.

MRI is now more commonly used in the preoperative setting for women with known or suspected endometriosis. This modality is not effective in detecting superficial endometriosis but more beneficial in assessing moderate to severe disease stages III–IV. The ability for MRI to diagnose endometriosis depends on the stromal to glandular consistency of the lesion, the extent of haemorrhage and inflammatory response [99]. Haemorrhage within the ovary is a key feature of endometriomas and MRI is commonly used to assess complex ovarian cysts found during ultrasound in which a

diagnosis is not certain. This has been shown to have high specificities of 92% but lower sensitivities of 67%, suggesting alternative pathologies share similar MRI characteristics [100].

The preoperative assessment and diagnosis of endometriosis stage III–IV is crucial for surgical planning to minimize the risk of complications in moderate to severe disease [101]. The identification of solid endometriotic nodules together with adhesions is well documented with MRI. In those lesions with pure fibrous components, images will elicit low signal intensity with T-1 and T-2-weighted images, whereas those with a heavy glandular component demonstrate high signal intensity with T-1 and T-2-weighted images. The commonest lesions found are a mixture of fibrous and glandular endometriosis but with stromal/fibrous predominance. These demonstrate low signal attenuation from the fibrous element, irregular speculated edges and cystic components with internal high signal intensity from areas of haemorrhage on T-1 images [102,103]. The specificities appeared to be consistently high [100,103–105], whereas sensitivities varied from 100 to 23% [103,106,107**] depending on the location of endometriosis deposit. The commonest location for deep infiltrating endometriosis to be found was the recto–cervical junction with high sensitivities (95%) and specificities (100%) [100,107**].

CONCLUSION

The preoperative diagnosis of endometriosis remains challenging for gynaecologists. The annual healthcare costs are estimated to be greater than diabetes for this chronic disease which impacts 10% of the female reproductive population [14]. With the average age of conception increasing, we will see disease progression and increased phenotypic expression. This will have an associated increase in health economic costs from surgery and fertility treatments unless noninvasive diagnostic tests become more accurate and accessible.

The development of a robust noninvasive test for endometriosis is of great clinical importance [19], yet it has many inherent difficulties related to cyclical hormonal fluctuations. The pathway that leads from a theory to the development of a diagnostic test is long, complicated and difficult [108]. Further understanding of the aetiology and basic science processes involved in the development of this disease will aid in the development of a noninvasive test.

The use of combined markers may provide improved accuracy levels while there is no single test available. Potential areas of promise include quantitative miRNA analysis.

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Conflicts of interest

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Music as an aid for postoperative recovery in adults: a systematic review and meta-analysis

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Summary

Background Music is a non-invasive, safe, and inexpensive intervention that can be delivered easily and successfully. We did a systematic review and meta-analysis to assess whether music improves recovery after surgical procedures.

Methods We included randomised controlled trials (RCTs) of adult patients undergoing surgical procedures, excluding those involving the central nervous system or head and neck, published in any language. We included RCTs in which any form of music initiated before, during, or after surgery was compared with standard care or other non-drug interventions. We searched MEDLINE, Embase, CINAHL, and Cochrane Central. We did meta-analysis with RevMan (version 5.2), with standardised mean differences (SMD) and random-effects models, and used Stata (version 12) for meta-regression. This study is registered with PROSPERO, number CRD42013005220.

Findings We identified 4261 titles and abstracts, and included 73 RCTs in the systematic review, with size varying between 20 and 458 participants. Choice of music, timing, and duration varied. Comparators included routine care, headphones with no music, white noise, and undisturbed bed rest. Music reduced postoperative pain (SMD −0·77 [95% CI −0·99 to −0·56]), anxiety (−0·68 [−0·95 to −0·41]), and analgesia use (−0·37 [−0·54 to −0·20]), and increased patient satisfaction (1·09 [0·51 to 1·68]), but length of stay did not differ (SMD −0·11 [−0·35 to 0·12]). Subgroup analyses showed that choice of music and timing of delivery made little difference to outcomes. Meta-regression identified no causes of heterogeneity in eight variables assessed. Music was effective even when patients were under general anaesthetic.

Interpretation Music could be offered as a way to help patients reduce pain and anxiety during the postoperative period. Timing and delivery can be adapted to individual clinical settings and medical teams.

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Introduction

Most people undergo a surgical procedure at some point in their lives—more than 51 million operative procedures are done every year in the USA,[1] and 4·6 million hospital admissions per year in England lead to surgical care.[2] A trend is emerging towards undertaking surgical procedures without general anaesthesia—for example, hysteroscopy and caesarean section. Irrespective of whether anaesthesia is used, the postoperative period is a difficult time for patients. The term postoperative recovery has not been precisely defined, but is clinical and includes restoration of the patient's cerebral and motor function. Surgical recovery strategies, such as Enhanced Recovery (a set of interventions aimed at improving patient outcomes and reducing their length of stay in hospital),[3–5] recommend several successful perioperative interventions. Some preoperative strategies, such as patient education and nutritional additives, reduce postoperative analgesia needs and improve patient satisfaction,[3–5] but not all potentially useful interventions have been assessed or incorporated.

Use of music to improve patients' hospital experience has a long history in medical care, including by Florence Nightingale.[6] Music was first described being used to help patients during operations by Evan Kane[7] in 1914. Several studies have investigated music's effect on emotions and neurophysiology.[8–10] Pre-recorded music through headphones, musical pillows, or background sound systems can be a non-invasive, safe, and inexpensive intervention compared with pharmaceuticals, and can be delivered easily and successfully in a medical setting.[11] Music has frequently been investigated in the context of recovery from operative procedures, and several randomised controlled trials (RCTs) have shown positive effects on patients' postoperative recovery.[12,13] This use of music differs from music therapy, which is a cognitive rehabilitation method.[14]

Previous systematic reviews have investigated music and its role in specific surgical procedures, such as colonoscopy,[15,16] or in only one aspect of patient experience in isolation, such as preoperative anxiety[17] or postoperative pain.[18,19] Cepeda and colleagues[20] investigated use of music for pain relief in both surgical and non-surgical settings. Nilsson[21] comprehensively reviewed 60 articles about use of music in the perioperative period but did not do a meta-analysis.[21] No previous reports have provided a comprehensive overview with meta-analyses and meta-regression.

At present, music is not used routinely perioperatively. Until now, scarcity of uptake might be due to ignorance or scepticism about the effectiveness of music.[22]

Despite the large number of relevant studies, music has not been implemented as a therapeutic intervention

For Enhanced Recovery see http://www.institute.nhs.uk/quality_and_service_improvement_tools/quality_and_service_improvement_tools/enhanced_recovery_programme.html

in everyday surgical practice because information about effectiveness has not been synthesised and disseminated universally. We assess effectiveness of music in improvement of postoperative recovery, incorporate all available RCTs, review effects of music on common outcome measures for postoperative care (pain, analgesia needs, anxiety, and length of stay), and investigate relevant subgroups (patient choice of music, timing of intervention, and whether general anaesthesia was used).

Methods

Search strategy and selection criteria

The predefined inclusion criteria were RCTs in any language with adult patients undergoing any form of surgical procedure (with or without sedation or anaesthesia) to any part of the body excluding the central nervous system or head and neck (because of potential hearing impairment). We compared any form of music initiated before, during, or after surgery with standard care or any other non-drug interventions such as massage, undisturbed rest, or relaxation. Outcomes of interest were: postoperative pain, analgesia needs, anxiety, infection rates, wound healing, costs, length of stay, and satisfaction with care. Analgesia use included any opioids or non-steroidal anti-inflammatory drugs (NSAIDs). If both were reported, we included opioid use in the meta-analyses. We measured outcomes up to 6 weeks postoperatively. We investigated subgroups of: pain before surgery and 4 h postoperatively; timing of intervention before, during, or after surgery; general anaesthetic versus no anaesthetic; and whether the patient was given choice of music. We recorded whether music given during surgery was started after induction of anaesthesia.

We searched the following databases: Medline (Jan 1, 1946–Oct 1, 2013), Embase (Jan 1, 1947–Oct 1, 2013), CINAHL (Jan 1, 1960–Oct 1, 2013), and Cochrane Central (Jan 1, 1898–Oct 1, 2013). We did keyword and MeSH searches for "music" or "music therapy" and any of the following: "surg*", "operat*", "recovery", "recuperation", "rehabilitation", "convalescence", or "post-op*". We checked reference lists of relevant reviews for additional studies. We transferred all relevant titles and abstracts to Endnote Web for assessment.

Data extraction and quality assessment

Two investigators (JH and MH) checked study eligibility. Both independently extracted data from studies using a standardised, predesigned extraction form in Microsoft Excel 2007. Disagreements were resolved through discussion or referral to a senior investigator (CM). We assessed quality of included studies with criteria set by The York Centre for Reviews and Dissemination,[21] focusing on randomisation, allocation concealment, presence of masking, explanation of withdrawals, and presence or absence of intention-to-treat analysis.

Statistical analysis

We tabulated characteristics and results of all included studies; analysis was quantitative. When standard errors or ranges were provided, standard deviations were calculated with standard formulae. We used Review Manager (version 5.2, Cochrane Library) for meta-analyses. We used random-effects models because of heterogeneity of participants and interventions. All outcomes were continuous measures, and we used standardised mean differences (SMD) when outcomes had differing measurement scales. Risk of publication bias was assessed by use of funnel plots. In addition to presenting SMD, which can be difficult to interpret clinically, we did back transformations of two outcomes (pain and anxiety) used in the included RCTs. We calculated back transformations with Microsoft Excel 2007. For the pain outcome, we used a mean of control group standard deviations from the RCTs measuring pain using a visual analogue scale (VAS). For the anxiety outcome, we used a mean of control group standard deviations from RCTs measuring anxiety with the state-trait anxiety inventory (STAI). To further investigate heterogeneity, we did meta-regressions with Stata version 12.

This study is registered with PROSPERO, number CRD42013005220.

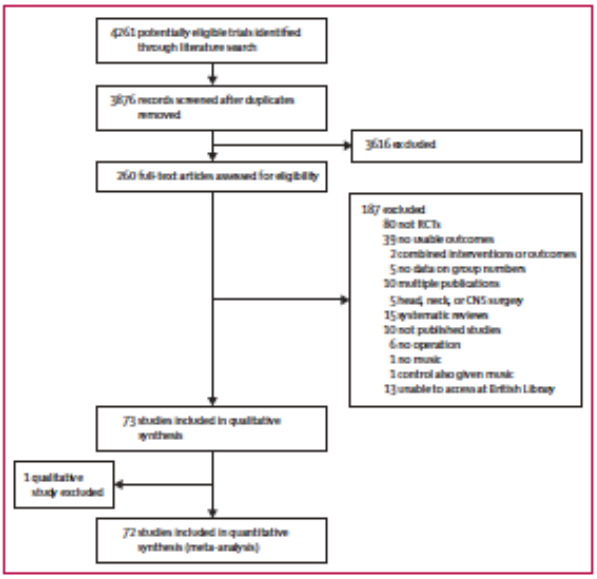

Figure 1: PRISMA flow diagram
RCT=randomised controlled trial. CNS=central nervous system.

Role of the funding source
There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 4261 titles and abstracts, of which we assessed 260 articles for inclusion (238 from database searches and 22 from reference lists; figure 1). We included 73 RCTs in the qualitative synthesis and 72 RCTs in quantitative syntheses (listed in the appendix), excluding one study that did not have quantitative data. Publication bias is not likely to have much effect on our findings because studies are evenly distributed either side of the SMD for postoperative pain (–0·77) (figure 2).

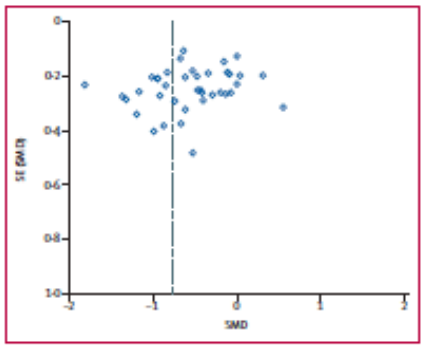

Figure 2: Funnel plot with pain outcome
SE=standard error. SMD=standardised mean difference.

Characteristics of included studies are shown in table 1. The size of the studies varied between 20 and 458 participants, and participants underwent various surgical procedures ranging from minor endoscopic interventions to transplantation surgery. Most studies included only elective procedures. Choice of music could be made by patient or researcher. Patients chose a wide variety of styles. Researchers identified single types of music such as Chinese classical music, or gave patients choice from a list of six or more styles. Most styles were soothing. Delivery could be by headphones or music pillows for patients only to hear or by loudspeakers, which could be heard by the medical team. Music delivered by headphones was often at a sufficiently low volume for patients to be able to communicate easily. Timing could be before, during, or after surgery, or a combination of these timings. Music could be played when patients were awake or anaesthetised. Duration of music varied between a few minutes to repeated episodes for several days. Comparator descriptions varied and included routine care, headphones with no music, white noise, and undisturbed bed rest. Duration and timing was usually similar to that of interventions. Outcomes included postoperative pain, analgesia needs, anxiety, length of stay, and satisfaction with care. None of the RCTs measured infection rates, wound healing, or costs. Some outcomes were measured during or soon after the procedure, others were measured at several times during the hospital stay.

Studies measured various outcomes (table 2). Pain was usually measured with VAS or numerical rating scales (NRS). An indirect measure of pain was use of analgesia, which varied substantially among studies, including paracetamol, opioid-based drugs such as pethidine, fentanyl, and morphine, and NSAIDs such as diclofenac and ibuprofen.

Quality of included studies varied (table 3), but several studies gave insufficient details to assess all aspects of quality. An intervention such as music cannot be masked to the patient unless the patient is under general anaesthesia; masking of investigators and outcome assessment is possible, but was not stated in many studies. When music was delivered to a patient under anaesthesia, whether masking was used was unclear.

Music reduced postoperative pain (45 RCTS, SMD –0·77 [95% CI –0·99 to –0·56]), anxiety (43 RCTS, –0·68 [–0·95 to –0·41]), and analgesia use (34 RCTS, –0·37 [–0·54 to –0·20]), and increased patient satisfaction (16 RCTS, 1·09 [0·51 to 1·68]), but did not affect length of stay (seven RCTs, –0·11 [–0·35 to 0·12]; figure 3). SMDs for the pain and anxiety outcomes were back calculated into specific measurements most used in the RCTs. Pain results (measured by 100 mm VAS) suggested that music reduced pain scores by 23 mm (95% CI 1·69–2·99) on average, compared with placebo. Anxiety results (measured by STAI on a scale of 20–80) were reduced by 6·4 units (3·86–8·94; on average, compared with placebo).

Heterogeneity was high for pain, anxiety, and analgesia use, with I^2 varying between 75% and 92%; heterogeneity for length of stay was 0%. No RCTs reported wound healing rates, costs, wound infections, or serious adverse events. A subgroup analysis by type of control (routine care *vs* control with attention) showed that type of control made no difference to effectiveness of music. Univariate meta-regression analysis to explain heterogeneity did not show a statistically significant effect of any of the eight variables (patient choice, timing of music, general anaesthetic, use of VAS to measure pain *vs* other pain measures, routine care *vs* other comparisons, endoscopy-type procedures *vs* surgery, allocation concealment, and masking of outcome assessment) on the pain outcome. Because we identified no significant outcomes by univariate meta-regression, we did not do multivariate meta-regression.

We categorised pragmatically into pain measured between 0 h and 4 h after surgery and pain measured more than 4 h after surgery. We identified no difference between pain measured at 0–4 h after surgery (SMD –0·79 [95% CI –1·06 to –0·52]) and pain

See Online for appendix

	Number of participants		Control groups	Procedure	General anaesthetic?	Music type	Patient choice?	Timing of delivery	Duration of music
	Intervention	Control							
Agwu and Olayemi (2006)	50	50	Routine care	Hysterosalpingography	No	Patient's own	Yes	Intraoperative	Duration of procedure
Allred et al (2010)	39	39	Rest period	Knee arthroplasty	Not specified	Easy listening	Yes	Postoperative	20 min
Angioli et al (2013)	185	187	Routine care	Hysteroscopy	No	Patient choice	Yes	Intraoperative	Duration of procedure
Argstatter et al (2006)	28 (music); 28 (music and coaching)	27	Routine care	Intracardiac catheterisation	No	Relaxation	No	Intraoperative	Duration of procedure
Ayoub et al (2005)	31	28 (operating room noise); 31 (white noise)	Operating room noise;white noise	Urological procedures	No	Urological procedure	Yes	Intraoperative	Duration of procedure
Bally et al (2003)	58	55	Routine care	Coronary angiography	No	Patient's own	Yes	Preoperative, intraoperative, and postoperative	Not specified
Barnason et al (1995)	33 (music); 29 (music and visual imaging)	34	Undisturbed bed rest	CABG	Yes	Soothing	Yes	Postoperative	30 min
Bechtold et al (2006)	85	81	Routine care	Colonoscopy	No	Watermark by Enya	No	Preoperative and intraoperative	Duration of procedure
Binns-Turner et al (2011)	15	15	Blank iPod	Mastectomy	Yes	Various	Yes	Preoperative and intraoperative	Duration of procedure
Blankfield et al (1995)	32 (music); 34 (music and therapeutic suggestion)	29	Blank cassette tape	CABG	Yes	Dream flight 2	No	Intraoperative and postoperative	Duration of procedure
Chan et al (2003)	112	108	Routine care	Colposcopy	No	Slow, rhythmic	No	Intraoperative	Duration of procedure
Chan (2007)	35	35	Undisturbed bed rest	C-clamp post PCI	No	Slow and soft	No	Intraoperative	45 min
Chlan et al (2000)	30	34	Routine care	Sigmoidoscopy	No	Various	Yes	Intraoperative	Duration of procedure
Colt et al (1999)	30	30	Headphones only	Bronchoscopy	No	Soft piano	No	Intraoperative	Duration of procedure
Costa et al (2010)	56	53	Mute headphones	Colonoscopy	No	Various	Yes	Preoperative and intraoperative	Duration of procedure; preoperative not specified
Cutshall et al (2011)	49	51	Bed rest	Cardiac surgery	Yes	Relaxing	Yes	Postoperative	20 min
Dunhauer et al (2007)	56	58 (routine care); 56 (guided imagery)	Routine care; guided imagery	Colposcopy	No	Relaxing	Yes	Intraoperative	Duration of procedure
Ebneshahidi and Mohseni (2008)	38	39	No music, headphones	Caesarean section	Not specified	Patient choice	Yes	Postoperative	30 min
Fredrikson et al (2009)	25 (music-ordinary sound-music); 25 (ordinary sound-music-ordinary sound)	–	–	Various	Not specified	Musicure	No	Postoperative	30 min per sound
Ghetti (2011)	9 (music); 11 (music and discussion)	9	Routine care	Transplant surgery	Yes	Instrumental	Yes	Postoperative	30-60 min
Good (1995)	21 (music); 21 (music and relaxation)	21 (routine care); 21 (jaw relaxation)	Routine care; jaw relaxation	Abdominal surgery	Yes	Sedative	Yes	Postoperative	2 min, and whenever else the patient chose
Good et al (1999)	122 (music); 109 (jaw relaxation)	111	Routine care	Abdominal surgery	Yes	Sedative	Yes	Postoperative	Before, during, and after ambulation

(Table 1 continues on next page)

	Number of participants		Control groups	Procedure	General anaesthetic?	Music type	Patient choice?	Timing of delivery	Duration of music
	Intervention	Control							
(Continued from previous page)									
Graewen and Sommer (2013)	40	35	Routine care	Laparascopic cholecystectomy	Yes	Soft music	No	Preoperative, intraoperative, and postoperative	Until patient discharge
Guerrero et al (2012)	54	47	Routine care	MVA abortion	No	Patient choice	Yes	Intraoperative	Duration of procedure
Harikumar et al (2006)	38	40	No music, headphones	Colonoscopy	No	Various	Yes	Intraoperative	Duration of procedure
Hook et al (2008)	51	51	Routine care	General abdominal	Yes	Various	Yes	Postoperative	8 x 30 min
Ilfer et al (2011)	25 (early postoperative music); 24 (late postoperative music)	25 (no music, headphones, early postoperatively); 27 (no music, headphones, late postoperatively); 25 (routine care)	No music, headphones early postoperatively; no music, headphones late postoperatively; routine care	Open cardiac surgery	Yes	Baroque	No	Postoperative	60 min
Ikonomidou et al (2004)	29	26	White noise, headphones	Lap sterilisation	Yes	Pan flute music	No	Preoperative and postoperative	30 min
Jafari et al (2012)	30	30	No music, headphones	CABG or valve repair	Yes	60–80 bpm	Yes	Preoperative and postoperative	30 min
Jimenez-Jimenez et al (2013)	20	20	Routine care	Varicose vein surgery	No	Classical	No	Intraoperative	Duration of procedure
Johnson (2012)	43	43	No music, headphones	Gynaecological surgery	Varies	Various	Yes	Preoperative	Not specified
Klempt (1999)	25 (music); 25 (hernioyne)	26	No music, headphones	General surgery	Yes	Classical	No	Intraoperative	Duration of procedure
Lee et al (2002)	55 (music and PCA)	55	Routine care and PCA	Colonoscopy	No	Various	Yes	Intraoperative	Duration of procedure
Lepage et al (2001)	25	25	Routine care	Ambulatory surgery	No	Various	Yes	Preoperative and postoperative	Not specified
Li et al (2011)	60	60	Routine care	Breast surgery	Yes	Patient choice	Yes	Postoperative	30 min twice daily
Li et al (2012)	30	30	Relaxation	LSCS	No	Chinese classical	Yes	Preoperative	30 min
Lopez-Cepero Andrada et al (2004)	63	55	Routine care	Colonoscopy	No	Classical	No	Preoperative and intraoperative	Duration of procedure
Maeyama et al (2005)	29	29	Routine care	Various	No	Classical	No	Intraoperative	Duration of procedure
McCaffrey and Locsin (2006)	62	62	Routine care	Lower limb orthopaedic	Yes	Various	Yes	Postoperative	Minimum 4 h daily
Migneault et al (2004)	15	15	No music, headphones	Open gynaecological	Yes	Various	Yes	Intraoperative	Duration of procedure
Mulooly et al (1988)	14	14	Routine care	Hysterectomy	Yes	Instrumental	No	Postoperative	10 min
Nilsson et al (2001)	30 (music); 31 (music and therapeutic suggestion)	34	Sound of operating room	Hysterectomy	Yes	Soothing	No	Intraoperative	Duration of procedure
Nilsson et al (2003a)	62 (music); 57 (music and therapeutic suggestion)	63	Blank tape, headphones	Hernia or varicose vein surgery	Yes	Soft instrumental	No	Postoperative	Patient requests cessation
Nilsson et al (2003b)	51 (intraoperative music, postoperative white noise); 1 (postoperative music, intraoperative white noise)	49	White noise	Hernia or varicose vein surgery	Yes	Instrumental	No	Intraoperative	Duration of procedure and 1 h after procedure

(Table 1 continues on next page)

	Number of participants		Control groups	Procedure	General anaesthetic?	Music type	Patient choice?	Timing of delivery	Duration of music
	Intervention	Control							
(Continued from previous page)									
Nilsson et al (2005)	25 (intraoperative music); 25 (postoperative music)	25	No music, headphones	Hernia repair	Yes	Relaxing	No	Intraoperative and postoperative	Duration of the procedure
Nilsson (2009a)	121	119	Routine care	Coronary angiography	No	Relaxing	No	Intraoperative	Duration of procedure
Nilsson (2009b)	28	30	Bed rest	Open CABG or valve replacement	Yes	Relaxing	No	Postoperative	30 min and 30 min rest
Nilsson et al (2009)	20	20	Routine care	Open CABG or valve replacement	Yes	Relaxing	No	Postoperative	30 min
Nilsson (2012)	34	34	Routine care	Coronary angiography	No	Musicure	No	Intraoperative	Duration of procedure
Ovayolu et al (2006)	30	30	Routine care	Colonoscopy	No	Turkish classical	No	Preoperative and intraoperative	30 min
Palakanis et al (1994)	25	25	Routine care	Sigmoidoscopy	No	Various	Yes	Intraoperative	Duration of procedure
Reza et al (2007)	50	50	White noise, headphones	Elective caesarean section	Yes	Spanish guitar	No	Intraoperative	Duration of procedure
Salmore and Nilsson (1995)	15 (OGD); 15 colonoscopy	33	Routine care	OGD and colonoscopy	No	Relaxing	No	Preoperative and intraoperative	Duration of procedure
Sen et al (2009)	30	30	No music, headphones	Urological procedures	No	Patient choice	Yes	Intraoperative	Duration of procedure
Sen et al (2010)	35	35	Routine care	Pfannenstiel LSCS	Yes	Patient choice	Yes	Postoperative	1 h
Serdelbach et al (2006)	50	36	Bed rest	Cardiac surgery	Yes	Easy listening	Yes	Postoperative	20 min twice daily for 3 days
Shabanloei et al (2010)	50	50	Routine care	Bone marrow biopsy	No	Relaxing	No	Intraoperative	Duration of procedure
Simcock et al (2008)	15	15	White noise, headphones	Knee arthroplasty	No	Patient choice	Yes	Intraoperative	Duration of procedure
Smolen et al (2002)	16	16	Routine care	Colonoscopy	No	Patient's own	Yes	Preoperative and intraoperative	Duration of procedure
Szmuk et al (2008)	20	20	No music, headphones	Laparoscopic hernia repair or cholecystectomy	Yes	Various	Yes	Intraoperative	Duration of procedure
Taylor-Piliae and Chair (2002)	15	15	Information about procedure	Cardiac catheterisation	No	Patient choice	Yes	Preoperative	15–20 min
Triller (2006)	93	107	Routine care	Bronchoscopy	No	Relaxation	No	Intraoperative	Duration of procedure
Tsivian et al (2012)	31	28	Routine care	Prostate biopsy	No	Classical	No	Intraoperative	Duration of procedure
Twiss et al (2006)	42	44	Routine care	CABG or valve surgery	Yes	Prescriptive	Yes	Intraoperative and postoperative	Duration of procedure and 3 days after procedure
Vachiramon et al (2013)	50	50	Routine care	Mohs surgery	No	Patient choice	Yes	Preoperative and intraoperative	Duration of procedure
Voss et al (2004)	20	21	Talking to staff	Open heart surgery	Yes	Sedative	Yes	Postoperative	30 min
Weeks and Nilsson (2011)	30 (music—loudspeaker); 34 (music pillow)	34	Routine care	Coronary angiogram or PCI	No	Musicure	No	Intraoperative	Duration of procedure
Wu et al (2013)	26	14	Routine care	Hand surgery	No	Patient choice	Yes	Preoperative and intraoperative	Not stated

(Table 1 continues on next page)

	Number of participants		Control groups	Procedure	General anaesthetic?	Music type	Patient choice?	Timing of delivery	Duration of music
	Intervention	Control							
(Continued from previous page)									
Wu et al (2012)	13	13	Routine care	Termination of pregnancy	No	Patient choice	Yes	Intraoperative	Duration of procedure
Yeo et al (2013)	35	35	No music, headphones	Cystoscopy	No	Classical	No	Intraoperative	Duration of procedure
Zengin et al (2013)	50	50	Routine care	Catheter placement	No	Turkish classical	No	Intraoperative	Duration of procedure
Zhang et al (2005)	55	55	No music, headphones	Hysterectomy	Yes	Calming	Yes	Intraoperative	Duration of procedure
Zimmerman et al (1996)	32 (music); 32 (music and video)	32	Routine care and rest	CABG	Yes	Patient choice	Yes	Postoperative	30 min

CABG=coronary artery bypass graft. PCI=percutaneous coronary intervention. Hemisync=a patented process used to create audio patterns designed to evoke effects on the brain. MVA=manual vacuum aspiration. bpm=beats per minute. PCA=patient-controlled analgesia. LSCS=lower segment Caesarean section. OGD=oesophagogastro-duodenoscopy. References are listed in the appendix.

Table 1: Study characteristics

measured more than 4 h after surgery (–0·76 [–1·19 to –0·33]; figure 3). The appendix contains individual subgroup meta-analyses.

When patients were allowed to choose the music (from personal choice or from a playlist) we noted a slightly increased but non-significant reduction in pain, compared with when patients had no choice (figure 3). Similarly, with patient choice, we recorded a small but non-significant reduction in analgesia use compared with when patients had no choice of music (figure 3). However, we recorded a slight but non-significant increase in anxiety when patients had a choice of music compared with when they had no choice (figure 3).

Pain seemed to be reduced most when music was played preoperatively (SMD –1·28 [–2·03 to –0·54]), then intraoperatively (–0·89 [–1·20 to –0·57]), and then postoperatively (–0·71 [–1·03 to –0·39]). We noted a similar pattern with analgesia use and anxiety. Analgesia use was reduced when music was played preoperatively (–0·43 [–0·67 to –0·20]), compared with intraoperatively (–0·41 [–0·70 to –0·12]), and postoperatively (–0·27 [–0·45 to –0·09]). Anxiety was likewise reduced when music was used preoperatively (–1·12 [–2·05 to –0·19]), compared with intraoperatively (–0·83 [–1·19 to –0·47]), and postoperatively (–0·50 [–0·96 to –0·04]).

Music reduced pain, even when given under general anaesthetic, but the intervention had an increased effect on pain when patients were conscious (SMD –1·05 [95% CI –1·45 to –0·64]) compared with under general anaesthetic (–0·49 [–0·74 to –0·25]). Similarly, music reduced analgesia use when given intraoperatively under general anaesthetic (SMD –0·58 [95% CI –1·05 to –0·11]) but had an increased effect when patients were conscious (–0·26 [–0·44 to –0·07]), and a similar effect was recorded for anxiety (–0·91 [–1·33 to –0·48] for music given under general anaesthetic *vs* –0·48 [–0·91 to –0·05] when patients were conscious).

None of the included studies reported side-effects. However, some studies reported that they ensured that the low volume at which music was delivered enabled communication with medical teams.

Discussion

Our systematic review and meta-analysis suggests that music played in the perioperative setting can reduce postoperative pain, anxiety, and analgesia needs, and improve patient satisfaction. However, we identified no difference in length of stay, although few studies measured it. None of the studies investigated effects of music on infections, wound healing rates, or costs.

We used wide inclusion criteria to make results more generalisable to clinical practice. One could argue that we should not have combined very heterogeneous studies because of clinical differences. For example, is meta-analysis of studies that used different analgesics worthwhile? Strong pain tends to be alleviated with strong analgesia, whereas mild pain responds to mild analgesia. Therefore, relative reduction in pain is of interest. We made the pragmatic decision that to combine all studies reporting analgesia use would be more useful clinically than to group specific types of analgesics. This decision was extended to other aspects of clinical heterogeneity such as age groups, types of interventions, and whether the intervention was done awake or under general anaesthesia. Measures of heterogeneity in the meta-analyses suggested a large amount of statistical heterogeneity in the main analyses for pain, analgesia use, and anxiety. To mitigate this effect, we used random-effects meta-analyses, although this approach only partly removes effects of heterogeneity.[34] Nevertheless, we considered that to combine data would provide a more clinically useful result than to include a small number of homogeneous studies. Because we combined clinically heterogeneous studies, we cannot be sure whether music applies equally to all clinical scenarios. However, we

	Pain score reported?	Analgesia use reported?	Anxiety score reported?	Length of stay reported?	Other outcome(s) reported?
Agwu and Okoye (2006)	No	No	Yes, STAI	No	Physiological parameters, HR and BP
Allred et al (2010)	Yes, VAS	No	Yes, VAS	No	No
Angioli et al (2013)	Yes, VAS	No	Yes, STAI	No	No
Argyriadou et al (2006)	No	No	Yes, STAI and VAS*	No	Physiological parameters, HR and BP
Ayoub et al (2005)	No	Yes, mg per drug	No	Yes, PACU admission length	No
Bally et al (2003)	Yes, VAS	Yes, mg per drug	Yes, STAI	No	No
Bamason et al (1995)	No	No	Yes, STAI	No	No
Bechtold et al (2006)	Yes, 100 mm VAS*	Yes, mg per drug*	No	No	Procedural time and difficulty questionnaire
Binns-Turner et al (2011)	Yes, VAS	No	Yes, SAI	No	Physiological parameters, HR and MAIBP
Blankfield et al (1995)	No	Yes, mg drug given postoperatively	No	Yes, total and ICU total	Depression score and ADLs
Chan et al (2003)	Yes, VAS	No	Yes, STAI	No	No
Chan (2007)	Yes, UCLA universal pain assessment method	No	No	No	No
Chlan et al (2000)	Yes, NRS	No	Yes, STAI	No	No
Colt et al (1999)	No	No	Yes, STAI	No	No
Costa et al (2010)	Yes, VAS	Yes, midazolam requests*	No	No	Patient satisfaction, Likert scale
Cutshall et al (2011)	Yes, VAS*	Yes, mg per drug	Yes, VAS*	No	Patient satisfaction, VAS*
Dantzer et al (2007)	Yes, VAS	No	Yes, STAI	No	No
Ebneshahidi and Mohseni (2008)	Yes, VAS	Yes, mg per drug	Yes, VAS	No	No
Fredrikson et al (2009)	No	No	No	No	Patient wellbeing†, Likert scale
Ghetti (2011)	Yes, NRS	No	No	No	Length of ambulation and patient satisfaction, PANAS
Good (1995)	Yes, PSD	Yes, mg per drug	Yes, STAI	No	No
Good et al (1999)	Yes, VAS	No	No	No	No
Gravenen (2013)	Yes, VAS	No	No	No	No
Guerrero et al (2012)	Yes, VAS	No	Yes, STAI	No	Physiological parameters, HR and BP
Harikumar et al (2006)	Yes, VAS	Yes, midazolam requests	No	Yes, recovery time	No
Hook et al (2008)	Yes, VAS PSD	Yes, morphine equi-analgesic dose	Yes, STAI and VAS†	No	No
Ibfelt et al (2011)	Yes, ANP	Yes, mg per drug	No	No	No
Ikonomidou et al (2004)	Yes, VAS	Yes, mg per drug	No	No	Patient wellbeing, VAS
Jafari et al (2012)	Yes, NRS	No	No	No	No
Jimenez-Jimenez et al (2013)	No	No	Yes, VAS	No	No
Johnson et al (2012)	No	No	Yes, STAI	Yes, time spent in PACU*	No
Klerman et al (1999)	No	Yes, mg per drug	No	No	No
Lee et al (2002)	Yes, VAS	Yes, PCA use and requests	No	Yes, recovery time†	Patient satisfaction, VAS
Lepage et al (2001)	No	Yes, midazolam requests	Yes, STAI and VAS	No	No
Li et al (2011)	Yes, VAS, PRI, and PPI	No	No	No	No
Li et al (2012)	Yes, VAS	No	Yes, Zung self-rated score	No	No
Lopez-Cepero Andrada et al (2004)	No	No	Yes, SAI and TAI*	No	No
Maeyama et al (2009)	No	Yes, mg per drug	Yes, STAI-SA	No	No
McCaffrey and Locsin (2006)	Yes, VAS	Yes, mg per drug	No	No	Patient satisfaction, NRS

(Table 2 continues on next page)

	Pain score reported?	Analgesia use reported?	Anxiety score reported?	Length of stay reported?	Other outcome(s) reported?
(Continued from previous page)					
Mignault et al (2004)	No	Yes, mg per drug		No	No
Mullooly et al (1988)	Yes, VAS	No	Yes, Likert scale	No	No
Nilsson et al (2001)	Yes, VAS	Yes, mg per drug	No	Yes, mobilisation time	Patient wellbeing and nausea, five-grade scale
Nilsson et al (2003a)	Yes, VAS	Yes, mg per drug	Yes, STAI	No	No
Nilsson et al (2003b)	Yes, NRS	Yes, mg per drug	Yes, questionnaire†	No	Patient satisfaction†, NRS
Nilsson et al (2005)	Yes, NRS	Yes, mg per drug	Yes, NRS	No	No
Nilsson (2005a)	Yes, NRS	Yes, mg per drug	Yes, STAI	No	No
Nilsson (2005b)	Yes, NRS	Yes, mg per drug		Yes, NRS*	No
Nilsson et al (2009)	No	Yes, mg per drug		No	Relaxation, NRS
Nilsson (2012)	No	Yes, mg per drug		Yes, NRS	Positive sound experience, NRS
Ovayolu et al (2006)	Yes, VAS	Yes, mg per drug		Yes, STAI	Patient satisfaction, VAS
Palakanis et al (1994)	No	No	Yes, STAI*	No	Physiological parameters, HR and MABP
Reza et al (2007)	Yes, VAS	Yes, mg per drug	Yes, VAS	No	Vomiting
Salmore and Nelson (1995)	No	Yes, mg per drug*	No	Yes, recovery time to discharge	No
Sen et al (2005)	No	Yes, mg per drug	No	Yes, recovery	Patient satisfaction, VAS
Sen et al (2010)	Yes, VAS	Yes, mg per drug	No	No	Patient satisfaction, VAS
Sendelbach et al (2006)	Yes, NRS*	Yes, mg per drug	Yes, state personality inventory*	No	No
Shabanloei et al (2010)	Yes, VAS	No	Yes, STAI	No	No
Simcock et al (2008)	Yes, VAS	No	No	No	Patient satisfaction, five-point scale
Smolen et al (2002)	No	Yes, mg per drug	Yes, SAI	No	No
Szmuk et al (2008)	Yes, VAS	No	No	Yes, time to eye opening	No
Taylor-Pilae and Chair (2002)	No	No	Yes, STAI	No	Patient satisfaction, various
Triller (2006)	No	No	No	No	Patient feeling, VAS
Tsivian et al (2012)	Yes, VAS	No	Yes, STAI*	No	No
Twiss et al (2006)	No	No	Yes, STAI	No	No
Vachiramon et al (2013)	No	No	Yes, STAI	No	No
Voss et al (2004)	Yes, VAS	No	Yes, VAS	No	No
Weeks and Nilsson (2011)	No	Yes, mg per drug	Yes, NRS	No	Patient wellbeing‡, questionnaire
Wu et al (2013)	No	No	Yes, VAS*	No	No
Wu et al (2012)	Yes, NRS*	No	Yes, NRS*	No	No
Yeo et al (2013)	Yes, VAS	No	Yes, STAI	No	Patient satisfaction, VAS
Zengin et al (2013)	Yes, VAS	No	Yes, STAI	No	No
Zhang et al (2005)	No	No	No	No	Patient satisfaction, VAS
Zimmerman et al (1996)	Yes, NRS	No	No	No	No

STAI=state-trait anxiety inventory. HR=heart rate. BP=blood pressure. VAS=visual analogue scale. SAI=state anxiety inventory. TAI=trait anxiety inventory. MABP=mean arterial blood pressure. ICU=intensive care unit. ADL=activities of daily living. UCLA=University of California at Los Angeles. PACU=post-anaesthesia care unit. PCA=patient-controlled analgesia. NRS=numerical rating scale. PANAS=positive and negative affect schedule. PSD=pain sensation and distress. ANP=anaesthesiological questionnaire for patients after anaesthesia. PRI=pain-rated index. PPI=present pain intensity. *Not included in numerical meta-analysis result because SD was not given. †Not included in data analysis (because of incomplete data or unusable format). References are listed in the appendix.

Table 2: Outcomes reported

investigated several clinically relevant subgroup analyses such as general anaesthesia versus no anaesthesia, timing, and choice of music versus no choice, and we did meta-regression. The heterogeneity is unexplained so an individual participant data (IPD) meta-analysis could be the next step.

The largest RCT recruited only 458 participants and assessment of whether a very large trial would generate similar results to this systematic review would be interesting. However, because many small trials showed positive effects of music in patients undergoing surgical procedures, a large trial might not be needed. These

	Method of randomisation	Allocation concealment	Blinding of participants	Blinding of investigators	Blinding of outcome assessment
Agwu and Okoye (2006)	Even/odd wrapped numbers	Not stated	No	Not stated	Not stated
Allred et al (2010)	Sealed envelope system	Yes	No	Not stated	Not stated
Angioli et al (2013)	Computer generated	Not stated	No	No	Not stated
Argintatter et al (2006)	Permuted block randomisation	Not stated	No	No	Not stated
Ayoub et al (2005)	Not stated	No	No	No	Yes
Bally et al (2003)	Randomly generated group numbers	Yes	No	Not stated	Not stated
Barnason et al (1995)	Drawing lots	Not stated	No	Not stated	Not stated
Bechtold et al (2006)	Opaque envelopes music or no music	Yes	Yes	No	No
Binns-Turner et al (2011)	Drawing numbers from bag	Not stated	No	Yes	Yes
Blankfield et al (1995)	Not stated	Not stated	Yes	Yes	Not stated
Chan et al (2003)	Computer generated	Yes	No	No	Not stated
Chan (2007)	Random digit randomiser	Not stated	No	No	No
Chlan et al (2000)	Coin toss	No	No	No	Not stated
Colt et al (1999)	Random number tables	Yes	Yes	Yes	Yes
Costa et al (2010)	Computer generated	Yes	No	Yes	Yes
Cutshall et al (2011)	Randomised using blocks	Yes	No	Not stated	Not stated
Danhauer et al (2007)	Random assignment slip	Not stated	No	Not stated	Not stated
Ebneshahidi and Mohseni (2008)	Not stated	Not stated	No	Not stated	Not stated
Fredriksson et al (2009)	Random envelopes	Not stated	No	Not stated	Not stated
Ghetti (2011)	Random number table	Not stated	No	Yes	Not stated
Good (1995)	Not stated	Not stated	No	Not stated	Not stated
Good et al (1999)	Computer generated	Not stated	No	No	Not stated
Graversen and Sommer (2013)	Random envelope	No	No	No	Not stated
Guerrero et al (2012)	Random number tables	Yes	No	Not stated	Not stated
Harikumar et al (2006)	Computer generated	Not stated	No	Yes	Not stated
Hook et al (2008)	Random envelopes	Not stated	No	Not stated	Not stated
Ibiher et al (2011)	Drawing lots	Not stated	No	No	No
Ikonomidou et al (2004)	Not stated	Yes	No	Yes	Not stated
Jafari et al (2012)	Not stated	Not stated	No	No	Yes
Jimenez-Jimenez et al (2013)	Computer generated	Not stated	No	No	Not stated
Johnson et al (2012)	Not stated	Not stated	No	Not stated	Not stated
Klernpt et al (1999)	Computer generated	Yes	Yes	Yes	Yes
Lee et al (2002)	Computer generated	Not stated	No	Yes	Not stated
Lepage et al (2001)	Not stated	Not stated	No	No	Not stated
Li et al (2011)	Computer generated	Not stated	No	Not stated	No
Li et al (2012)	Computer generated	No	No	No	No
López-Cepero Andrada et al (2004)	Coin toss	No	No	No	Not stated
Maeyama et al (2009)	Not stated	Not stated	No	No	Not stated
McCaffrey and Locsin (2006)	By room availability	Yes	No	No	Not stated
Migneault et al (2004)	Not stated	Not stated	Yes	Yes	Not stated
Mullooly et al (1988)	Not stated	Not stated	No	Not stated	Not stated
Nilsson et al (2001)	Computer generated	Not stated	Yes	Not stated	Not stated
Nilsson et al (2003a)	Computer generated	No	No	No	Not stated
Nilsson et al (2003b)	Computer generated	Not stated	Yes	Not stated	Not stated
Nilsson et al (2005)	Computer generated	Not stated	Yes	Yes	Not stated
Nilsson (2009a)	Computer generated	No	No	No	Not stated
Nilsson (2009b)	Computer generated	Not stated	No	Yes	Yes
Nilsson et al (2009)	Computer generated	Not stated	No	Yes	Yes
Nilsson (2012)	Computer generated	Not stated	No	Not stated	Not stated
Ovayolu et al (2006)	Computer generated random numbers	No	No	No	Not stated

(Table 3 continues on next page)

	Method of randomisation	Allocation concealment	Blinding of participants	Blinding of investigators	Blinding of outcome assessment
(Continued from page)					
Palakanis et al (1994)	Coin toss	Not stated	No	Not stated	Not stated
Reza et al (2007)	Computer generated	Yes	Yes	Yes	Yes
Salmore and Nelson (1999)	Not stated	Not stated	No	No	Not stated
Sen et al (2009)	Computer generated	Not stated	No	No	Not stated
Sen et al (2010)	Computer generated	Not stated	No	No	Not stated
Serdelbach et al (2006)	Coin toss	Not stated	No	Not stated	Not stated
Shabanloei et al (2010)	Random number table	Not stated	No	No	Not stated
Simcock et al (2008)	Sealed envelopes	Yes	Yes	Yes	Not stated
Smolen et al (2002)	Not stated	No	No	No	Not stated
Szmuk et al (2008)	Not stated	Yes	Yes	Yes	Not stated
Taylor-Piliae and Chair (2002)	Drawing slip of paper	Not stated	No	No	No
Triller (2006)	Not stated	Not stated	No	Not stated	Not stated
Tsivian et al (2012)	Adapted coin toss	No	No	No	Not stated
Twiss et al (2006)	Drawing slip of paper	Not stated	No	Not stated	Not stated
Vachiramon et al (2013)	Randomised number table	Not stated	No	No	Not stated
Voss et al (2004)	Varied block size	Yes	No	No	Not stated
Weeks and Nilsson (2011)	Sealed envelopes	Yes	No	No	Not stated
Wu et al (2013)	Concealed envelopes	Yes	No	No	Not stated
Wu et al (2012)	Computer generated	Yes	No	No	Yes
Yeo et al (2013)	Block randomised	No	No	Not stated	Not stated
Zengin et al (2013)	Computer generated	Not stated	No	Not stated	Not stated
Zhang et al (2005)	Computer generated	Not stated	Yes	Not stated	Not stated
Zimmerman et al (1996)	Not stated	Not stated	No	Not stated	Not stated

Table 3: Study quality

small RCTs were difficult to find in journals that are not well known, which shows the benefits of systemic reviews and meta-analyses. However, a large RCT would address issues of heterogeneity.

Prediction intervals could have been calculated because they would give a more comprehensive view of potential effects of music in individual settings. However, prediction intervals tend to be wider than 95% CIs and, because of clinical heterogeneity, how calculation of prediction intervals would help to guide individual clinicians on implementation of music is unclear.

We included more studies than have previous systematic reviews. The most comprehensive previous systematic review used a vote-counting approach to summarise results only.[11] Some of the previous systematic reviews investigated only one outcome, such as anxiety or pain, whereas we report all relevant clinical outcomes. We believe that this study is the most comprehensive systematic review and meta-analysis so far for use of music in perioperative settings, including 6902 patients. Our results are similar to those of Cepeda and colleagues[10] for effect size. We identified no side-effects reported in any of the studies, as did a Cochrane review.[21]

The beneficial effects of music on patient wellbeing are consistent with expectations and the public's perception of music. Several potential mechanisms could help to explain effects of music from the patient's and the medical team's perspective. Modern theories of pain suggest that pain experience is affected by physical and psychological factors. Cognitive activities such as listening to music can affect perceived intensity and unpleasantness of pain, enabling patients' sensation of pain to be reduced.[26] Another potential mechanism could be reduced autonomic nervous system activity, such as reduced pulse and respiration rate and decreased blood pressure.[27] For patients undergoing general anaesthesia, some evidence from RCTs suggests that parts of the brain involved in hearing can sometimes be perceptive during general anaesthetic.[28] For about one in 1000 people undergoing general anaesthesia, unwanted intraoperative awareness during anaesthetic is a risk factor for post-traumatic stress.[29] Whether intraoperative music might have prevented this effect by reduction of anxiety is unclear. Whether other distracting stimuli might have a similar effect to music, such as videos or talking books, is unclear. Some experimental evidence shows that distraction with video gaming can reduce experimentally induced pain in adults,[30] but no studies have been done to investigate the effectiveness of talking radio or talking books during surgery in the adult population.

Other primary studies and systematic reviews have shown that medical teams might be more relaxed and attentive[31] when music that they enjoy is playing, but use of music might be inappropriate in some settings. The medical team might be distracted if music is audible from the patient's headphones. Music might impede

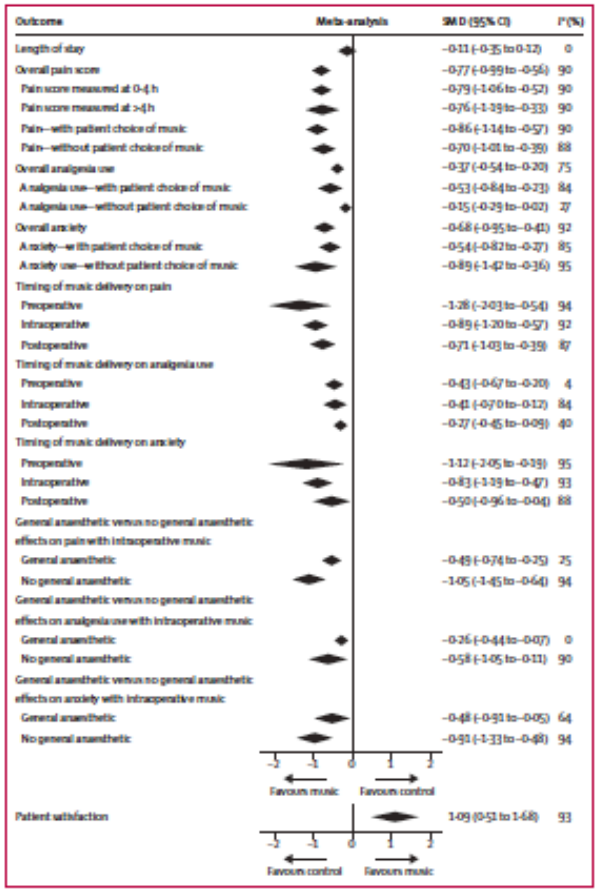

Figure 3: Summary forest plot
SMD=standardised mean difference. References listed in the appendix.

communication with patients, especially during an awake procedure. If patients need to be able to communicate with health-care workers, bilateral headphone use might be an obstacle. Music and noise could potentially obstruct other interventions through negatively affecting the surgeon's performance. Therefore, music should not be imposed on the medical team, especially during the procedure. If medical teams intend to introduce music into perioperative settings, care needs to be taken that music does not interfere with communication among the medical team.[11,13]

Music is a non-invasive, safe, and inexpensive intervention that can be delivered easily and successfully in a hospital setting. We believe that sufficient research has been done to show that music should be available to all patients undergoing operative procedures. Patients should be able to choose the type of music they would like to hear, but whether this music should be of their own choice or from a playlist is unclear. However, some patients might prefer for religious reasons to listen to recitations or natural sounds. Timing of music does not make much difference to outcomes so can be adapted to the individual clinical setting and medical team. For example, some medical teams might want to implement intraoperative music, whereas other teams might prefer the patient to listen to their own electronic musical device before the procedure or as soon as they arrive back onto the ward. The appropriate volume for use in different settings is likewise unclear.

Obstacles to implementation in the clinical setting, such as copyright and intellectual property issues, need investigation. On a local scale, patients could be encouraged to listen to music through patient information leaflets and hospital guidelines.

Contributors
EB and CM came up with the research idea. Statistical supervision was provided by CM, and senior clinical input by EB. CM, MH, and JH designed the protocol. MH and JH did searches, study selection, and subgroup analysis. All authors wrote the report.

Declaration of interests
We declare no competing interests.

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GYNECOLOGY

Variation in outcome reporting in endometriosis trials: a systematic review

WORKING TOWARDS ENDORSEMENT FROM CROWN CORE OUTCOMES IN WOMEN'S HEALTH

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OBJECTIVE: We reviewed the outcomes and outcome measures reported in randomized controlled trials and their relationship with methodological quality, year of publication, commercial funding, and journal impact factor.

DATA SOURCES: We searched the following sources: (1) Cochrane Central Register of Controlled Trials, (2) Embase, and (3) MEDLINE from inception to November 2014.

STUDY ELIGIBILITY: We included all randomized controlled trials evaluating a surgical intervention with or without a medical adjuvant therapy for the treatment of endometriosis symptoms.

STUDY DESIGN: Two authors independently selected trials, assessed methodological quality (Jadad score; range, 1-5), outcome reporting quality (Management of Otitis Media with Effusion in Cleft Palate criteria; range, 1-6), year of publication, impact factor in the year of publication, and commercial funding (yes or no). Univariate and bivariate analyses were performed using Spearman Rh and Mann-Whitney *U* tests. We used a multivariate linear regression model to assess relationship associations between outcome reporting quality and other variables.

RESULTS: There were 54 randomized controlled trials (5427 participants), which reported 164 outcomes and 113 outcome measures. The 3 most commonly reported primary outcomes were dysmenorrhea (10 outcome measures; 23 trials), dyspareunia (11 outcome measures; 21 trials), and pregnancy (3 outcome measures; 26 trials). The median quality of outcome reporting was 3 (interquartile range 4–2) and methodological quality 3 (interquartile range 5–2). Multivariate linear regression demonstrated a relationship between outcome reporting quality with methodological quality ($\beta = 0.325$; $P = .038$) and year of publication ($\beta = 0.067$; $P = .040$). No relationship was demonstrated between outcome reporting quality with journal impact factor (Rho = 0.190; $P = .212$) or commercial funding ($P = .370$).

CONCLUSION: Variation in outcome reporting within published endometriosis trials prohibits comparison, combination, and synthesis of data. This limits the usefulness of research to inform clinical practice, enhance patient care, and improve patient outcomes. In the absence of a core outcome set for endometriosis we recommend the use of the 3 most common pain (dysmenorrhea, dyspareunia, and pelvic pain) and subfertility (pregnancy, miscarriage, and live birth) outcomes. International consensus among stakeholders is needed to establish a core outcome set for endometriosis trials.

Key words: core-outcome sets, endometriosis, outcome harmonization, outcome variation

Endometriosis affects 1 in 10 women and impairs health related quality of life in the domains of fertility, pain, psychological, and social functioning. Endometriosis is poorly understood and is currently managed with holistic, medical, and surgical interventions. There is no consensus among patients, health care professionals, and researchers regarding the outcomes and outcome measures that should be collected and reported in endometriosis trials assessing potential interventions.

The factors linked to outcome reporting variation are unclear. Without consensus, the variation in outcome reporting within effectiveness trials produces misleading results as individual studies cannot be compared or combined, favoring ineffective interventions or underestimating harms.[1,2] The accurate measurement and reporting of consistent comparable outcomes is crucial.

In line with recommendations from the US Congress established Patient-Centered Outcomes Research Institute; this review will help toward ensuring the selection of "outcomes that people in the population of interest notice and care about."[3]

We aimed to systematically organize and describe the outcomes and their measurement instruments and definitions reported by randomized controlled trials (RCTs) evaluating the surgical

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interventions for endometriosis. We evaluated the methodological and outcome reporting quality of those studies. Finally, we aimed to assess whether publication features such as journal impact factor, year of publication, methodological quality, and publication location (general or women's health–specific journal) are correlated to outcome reporting or methodological quality.

Materials and Methods

Sources

A protocol with explicitly defined objectives, criteria for study selection, and approaches assessing outcome selection was developed. The systematic review was registered with the Core Outcome Measures in Effectiveness Trials Initiative Register[4] and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[5]

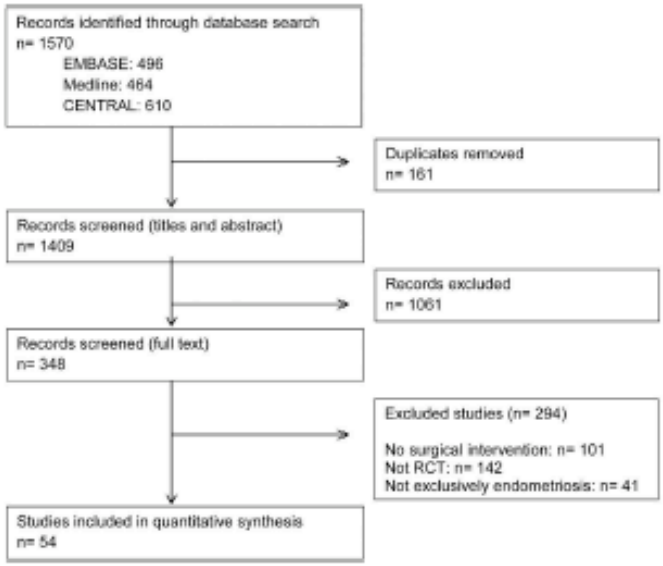
A comprehensive and systematic literature review was undertaken searching the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and Medline from database inception to November 2014 (see Appendix). We searched the Cochrane Register of Systematic reviews to identify relevant Cochrane systematic reviews searching the bibliography for eligible trials.[6]

Study selection

Two reviewers (M.H. and J.M.D.) independently screened titles and abstracts. They critically reviewed the full text of selected studies to assess eligibility. Any discrepancies between the reviewers were resolved by discussion with a third author (K.S.K.). We included randomized control trials assessing the effectiveness of any surgical intervention with or without an adjuvant medical therapy for the treatment of pain and subfertility associated with endometriosis. We excluded quasi-randomized, nonrandomized, analytical, and diagnostic studies.

Two reviewers (M.H. and J.D.) extracted the data independently using a piloted data extraction sheet. The study characteristics were extracted from the trial report including the publishing journal, study design, setting, participants, interventions, sample size calculation, and the pharmaceutical funding. The impact factor in the year of publication was identified by reviewing data provided by Researchgate. We systematically reviewed primary and secondary outcomes and their definitions and instruments. The study characteristics and outcomes were summarized in tabular form and presented with descriptive statistics within summary tables and diagrams (Table 1).

FIGURE 1
Outcome reporting in endometriosis trials: flow of included studies



CENTRAL, Cochrane Central Register of Controlled Trials; *RCT*, randomized controlled trial.

Hirsch. Outcome reporting in endometriosis trials. Am J Obstet Gynecol 2016.

Quality assessment

Two reviewers (M.H. and J.D.) independently assessed each study's methodological quality using the JADAD criteria. The 5 point validated scoring system assesses the following: (1) was the trial described as randomized (1 point); (2) did the trial use an appropriate method of randomization (1 point); (3) was the trial blinded (1 point); (4) did the trial use an appropriate method of blinding? (1 point); and (5) did the trial account for all patients randomized (1 point)?[7]

Two reviewers (M.H. and J.D.) independently assessed each study's outcome reporting using the 6 point Management of Otitis Media with Effusion in Cleft Palate scoring system validated for the development of a core outcome set[8]: (1) was a primary outcome stated (1 point); (2) was the primary outcome clearly defined for reproducible measures (1 point); (3) were the secondary outcomes clearly stated (1 point); (4) were the secondary outcomes clearly defined for reproducible measures (1 point); (5) do the authors explain the choice of outcome (1 point); and (6) are the methods used designed to enhance quality of measures appropriate (1 point)? There is no defined rating score; therefore, a previously used cutoff value of ≥ 4 was used to represent high-quality trials.[8]

Analysis

Univariate association between continuous factors was assessed by nonparametric correlation coefficient (Spearman rho). The comparison of

TABLE 1
Outcome reporting in endometriosis trials: study characteristics

Study	IF	Method quality	Outcome quality	Intervention group 1	Intervention group 2	Intervention group 3
Abbott et al, 2004[9]	3.17	5	4	Diagnostic laparoscopy plus delayed surgical treatment	Surgical treatment plus repeat surgery	
Abu Hashim et al, 2012[10]	1.85	5	6	Surgical treatment plus superovulation with letrozole plus intrauterine insemination	Surgical treatment plus superovulation with clomiphene citrate plus intrauterine insemination	
Adién et al, 2002[11]	3.202	2	2	Surgical treatment plus interferon α-2b	Surgical treatment plus saline	
Alborzi et al, 2004[12]	3.17	2	5	Surgical treatment plus ovarian fenestration and coagulation	Surgical treatment plus ovarian cystectomy	
Alborzi et al, 2007[13]	3.168	2	2	Surgical treatment plus ovarian fenestration and coagulation	Surgical treatment plus ovarian cystectomy	Surgical treatment plus ovarian fenestration and cystectomy
Alborzi et al, 2011[14]	1.072	2	2	Surgical treatment plus GnRHa	Surgical treatment plus aromatase inhibitor	Surgical treatment
Alkatout et al, 2013[15]	1.575	2	2	Surgical treatment	HT	Surgical treatment plus hormone therapy
Audebert et al, 1998[16]	0.745	2	2	Surgery treatment plus GnRHa	GnRHa plus surgical treatment	
Ballester et al, 2011[17]	3.468	2	4	Laparoscopy plus colorectal resection	Laparotomy plus colorectal resection	
Beretta et al, 1998[18]	3.344	2	2	Surgical treatment plus ovarian cystectomy	Surgical treatment plus ovarian fenestration and coagulation	
Bianchi et al, 1999[19]	3.643	3	2	Surgical treatment plus danocrine	Surgical treatment	
Busacca et al, 2001[20]	2.751	3	2	Surgical treatment plus GnRH agonist	Surgical treatment	
Candiani et al, 1992[21]	1.982	3	3	Surgical treatment plus presacral neurectomy	Surgical treatment	
Cobellis et al, 2011[22]	1.974	5	3	Surgery treatment plus fatty acid amide	Surgical treatment plus selective COX2 NSAID	Surgical treatment
Cosson et al, 2002[23]	3.202	3	4	Surgical treatment plus progestin	Surgical treatment plus GnRHa	
Costello et al, 2010[24]	3.122	5	6	Surgical treatment plus multimodal intraoperative analgesia	Surgical treatment plus placebo	

Hirsch. Outcome reporting in endometriosis trials. Am J Obstet Gynecol 2016.

(continued)

TABLE 1
Outcome reporting in endometriosis trials: study characteristics (continued)

Study	IF	Method quality	Outcome quality	Intervention group 1	Intervention group 2	Intervention group 3
Creus et al, 2008[25]	2.537	5	0	Surgical treatment plus xanthine derivative	Surgical treatment plus placebo	
Darai et al, 2010[26]	7.474	3	5	Laparoscopy plus colorectal resection	Laparotomy plus colorectal resection	
Darai et al, 2011[27]	3.564	3	2	Laparoscopy plus colorectal resection	Laparotomy plus colorectal resection	
diZerega et al, 2007[28]	3.168	5	3	Surgical treatment plus adhesion barrier gel	Surgical treatment	
Healey et al, 2010[29]	3.122	5	3	Surgical treatment plus ablation	Surgical treatment plus excision	
Hoo et al, 2014[30]	3.483	5	6	Surgical treatment plus ovarian suspension	Surgical treatment	
Jarrell et al, 2005[31]	—	5	2	Surgical treatment	Diagnostic laparoscopy plus biopsy	
Kamencic et al, 2008[32]	—	3	2	Surgical treatment plus xanthine derivative	Surgical treatment	
Koninckx et al, 2013[33]	2.03	5	6	Surgical treatment plus humidified CO_2 pneumoperitoneum	Surgical treatment plus peritoneal full conditioning and barrier gel	
Lalchandani et al, 2005[34]	—	2	3	Diagnostic laparoscopy plus GnRHa plus HT	Surgical treatment plus helium thermal coagulator	
Loverro et al, 2008[35]	1.565	5	2	Surgical treatment plus GnRHa	Surgical treatment plus placebo	
Mais et al, 1995[36]	—	2	5	Surgical treatment plus adhesion barrier	Surgical treatment	
Marcoux et al, 1997[37]	27.766	5	6	Surgical treatment plus ablation	Surgical treatment plus excision	
Matorras et al, 2002[38]	3.202	2	2	Bilateral salpingo-oophrectomy plus HT	Bilateral salpingo-oophrectomy	
Moini et al, 2012[39]	0.471	5	4	Surgical treatment	Diagnostic Laparoscopy	
Morgante et al, 1999[40]	3.643	2	3	Surgical treatment plus GnRHa plus danocrine	Surgical treatment plus GnRHa	
Nowroozi et al, 1987[41]	—	3	1	Surgical treatment plus ablation	Diagnostic laparoscopy	

Hirsch. Outcome reporting in endometriosis trials. Am J Obstet Gynecol 2016. (continued)

TABLE 1
Outcome reporting in endometriosis trials: study characteristics (continued)

Study	IF	Method quality	Outcome quality	Intervention group 1	Intervention group 2	Intervention group 3
Parazzini et al, 1994[42]	2.247	5	3	Surgical treatment plus GnRHa	Surgical treatment	
Parazzini et al, 1999[43]	3.643	3	2	Surgical treatment plus ablation	Surgical treatment plus excision	Diagnostic laparoscopy
Seller et al, 1986[44]	—	3	0	Surgical treatment plus ablation	Treatment with danocrine	
Soysal et al, 2004[45]	3.072	5	4	Surgical treatment plus GnRHa	Surgical treatment plus GnRHa plus aromatase inhibitor	
Surrey et al, 1994[46]	—	2	3	GIFT plus surgical treatment	GIFT	
Sutton et al, 1994[47]	2.464	5	3	Surgical treatment plus presacral neurectomy	Diagnostic laparoscopy	
Sutton et al, 1997[48]	2.612	4	2	Surgical treatment plus presacral neurectomy	Diagnostic laparoscopy	
Sutton et al, 2001[49]	0.63	5	2	Surgical treatment plus presacral neurectomy	Surgical treatment	
Tanmahasamut et al, 2012[50]	4.798	5	5	Surgical treatment plus Mirena IUS	Surgical treatment	
Telimaa et al, 1988[51]	—	4	1	Surgical treatment plus danocrine	Surgical treatment plus progestin	Surgical treatment plus placebo
Tsai et al, 2004[52]	0.778	5	2	Surgical treatment plus GnRHa	Surgical treatment plus danocrine	Surgical treatment
Vercellini et al, 1999[53]	2.657	3	4	Surgical treatment plus GnRHa	Surgical treatment	
Vercellini et al, 2002[54]	3.202	3	4	Surgical treatment plus progestin	Surgical treatment plus COCP	
Vercellini et al, 2003[55]	3.483	5	5	Surgical treatment plus presacral neurectomy	Surgical treatment	
Vercellini et al, 2003[56]	3.483	3	3	Surgical treatment plus Mirena IUS	Surgical treatment	
Wickström et al, 2012[57]	4.542	5	3	Tubal pertubation plus lidocaine	Tubal pertubation plus placebo	
Wright et al, 2005[58]	3.114	4	2	Surgical treatment plus ablation	Surgical treatment plus excision	

Hirsch. Outcome reporting in endometriosis trials. Am J Obstet Gynecol 2016. (continued)

TABLE 1
Outcome reporting in endometriosis trials: study characteristics *(continued)*

Study	IF	Method quality	Outcome quality	Intervention group 1	Intervention group 2	Intervention group 3
Zhao et al, 2013[59]	1.401	1	2	Surgical treatment plus Chinese medicine	Surgical treatment plus GnRHa plus HT	Surgical treatment plus progestin
Zhao et al, 2013[60]	1.401	3	6	Surgical treatment plus Chinese medicine	Surgical treatment plus GnRHa plus HT	Surgical treatment plus progestin
Zhu et al, 2014[61]	1.877	3	2	Surgical treatment plus COCP	Surgical treatment plus COCP plus Chinese medicine	Surgical treatment
Zullo et al, 2003[62]	2.518	5	4	Surgical treatment plus presacral neurectomy	Surgical treatment	

COCP, combined oral contraceptive pill; *COX*, cyclooxygenase; *IF*, impact factor; *GnRHa*, gonadotropin-releasing hormone agonist; *HT*, hormone therapy; *IF*, impact factor; *IUI*, intrauterine insemination; *NSAID*, nonsteroidal anti-inflammatory drug.

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outcome reporting quality was assessed between groups according to type of journal (general vs specialist), funding source (commercial or other), year of publication, and impact factor in the year of publication. Journals specific to obstetrics and gynecology as listed by www.scimagojr.com were classified as specialist. Funding status was identified in the article text including commercial funding or the donation of equipment, which had facilitated the trial. These univariate analyses were performed using nonparametric Mann Whitney *U* tests.

To assess the multivariate relationship with quality of outcome reporting, we used a multivariate linear regression model including journal type, impact factor in the year of publication, year of publication, and methodological quality as independent variables and outcome reporting as the dependent variable. Only significant predictors were retained in the final model. We globally checked linear regression assumptions by exploring residuals vs predicted plot. All the analyses were performed using Stata program (StataCorp, 2013, Stata Statistical Software, release 13; StataCorp LP, College Station, TX).

Results

The search strategy identified 1570 titles and abstracts. We screened 1409 titles and abstracts following the exclusion of 161 duplicate records (Figure 1). We included 54 RCTs[9–62] (Table 1). The included trials collected and reported 164 outcomes and 113 outcome measures (Table 2). Unfortunately, the outcome measurement or definition was not described within the trial report for 110 outcomes.

The most common outcome domains were pain (29 of 54 trials [53%]), subfertility (22 of 54 trials [41%]), and quality of life (9 of 54 trials [17%]). When considering the pain domain, commonly reported pain outcomes were dysmenorrhea (23 RCTs, 10 outcome measures), dyspareunia (21 RCTs, 11 outcome measures), and pelvic pain (15 RCTs, 9 outcome measures). Three trials did not specify the outcome

TABLE 2
Outcome reporting in endometriosis trials: outcome and outcome measures reported

Domain	RCTs	Outcomes	Outcome measure
Pain	37	32	24
Subfertility	32	28	11
Quality of life	9	10	10
Surgical adverse events	14	34	5
Medical adverse events	8	22	0

RCT, randomized controlled trial.

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TABLE 3
Outcome reporting in endometriosis trials: reported pain and fertility outcomes

Outcome domain	Outcome	Trials, n
Fertility outcomes	Pregnancy	26
	Miscarriage	7
	Live birth	5
	Estradiol	5
	Ectopic pregnancy	4
	Endometrial thickness	2
	Number of follicles > 18 mm	3
	Ampules of gonadotropin	1
	Days of stimulation	1
	Early fetal loss	1
	Embryos per cycle	1
	Follicular-stimulating hormone	1
	Luteinizing hormone	1
	Number of oocytes per cycle	1
	Pregnancy interval	1
	Pregnancy subsequent cycle	1
	Reproductive outcome	1
	Singleton delivery	1
	Stillbirth	1
	Term delivery	2
	Twin delivery	1
	Twin pregnancy	1
	Vaginal delivery	1
Pain outcomes	Dysmenorrhea	23
	Dyspareunia	21
	Pelvic pain	15

Hirsch. Outcome reporting in endometriosis trials. Am J Obstet Gynecol 2016. (continued)

measure used to assess pain[16,26,27] (Tables 2–4).

Dysmenorrhea was measured by 10 different outcome measures: a visual analog scale anchored between 0 and 10; a visual analog scale anchored between 0 and 100; a visual analog scale anchored between 0 (no pain) and 10 (severe pain); a visual analog scale with no specified parameters; a questionnaire including 3 domains of activities of daily living, coexistence of systemic symptoms, and analgesic requirement; a questionnaire with ranked symptoms; a questionnaire with no further description available; a ranked ordinal scale (1–5); number of episodes; and not specified.

The 3 most commonly reported fertility outcomes were pregnancy (26 RCTs, 5 outcome measures), miscarriage (7 RCTs, 2 outcome measures), and live birth (5 RCTs, 2 outcome measures). Pregnancy was measured with the following outcome measures: ultrasound scan visualizing fetal heart; ultrasound growth scan; serum beta HCG; pregnancy greater than 20 weeks' gestation; not specified (Tables 3 and 4 and Figure 2).

Quality of life was reported by 9 trials using 10 different outcome measures including the World Health Organization Quality of Life-BREF; the EuroQol-5D; the Short-Form Health Survey 12; the Short-Form Health Survey 36; the Hospital Anxiety and Depression Scale; the Greene Climacteric Scale; the Blatt Kupperman Menopausal Index; the Sabbatsberg Sexual Rating Scale; the revised Sabbatsberg Sexual Rating Scale; and the Sexual Activity Questionnaire.[9,17,26,27,45,50,54,55,60]

Intraoperative and postoperative complications were collected and reported by 14 RCTs using 25 different outcomes and 5 different outcome measures.[12,21,23,26–29,32,33,36,37,39,41,62]

The median outcome reporting quality was 3 of 6 (interquartile range 4–2) and methodological quality 3 of 5 (interquartile range 5–2). Table 1 summarizes quality assessment. Just more than half of all trials clearly reported a primary outcome (32 of

54),[10-12,15,18,21,23,24,26-30,33,34,36,37,39,43,45-47,50,53-57,59-62] whereas just less than half (26 of 54)[9,10,20,21,24,26,27,30-34,37,39,43,45,49,50,52,53-55,57,60-62] described using a power calculation to influence their sample size.

The majority of studies, 89% (n = 48 of 54), were published in an obstetrics and gynecology–specific journal, whereas 11% of the trials (n = 6 of 54) were published in general medical journals including 1 trial in *The New England Journal of Medicine*.[37] Studies receiving commercial or pharmaceutical funding accounted for 22% of the trials (n = 12 of 54),[16,24,25,29-31,33,37-39,50,57] whereas 4% of the trials (n = 2 of 54)[10,32] did not receive funding and 74% of the trials (n = 40) did not specify whether they received private funding.[9,11-15,17-23,26-28,34-36,40-49,51-56,58-62]

We explored the relationship between quality of outcome reporting with the impact factor in the year of publication, study quality, year of publication, journal type, and commercial funding (Table 5). After exploring the data, we found 1 study[37] behaving clearly differently from the other studies in terms of impact factor (impact factor = 27.776). This outlier was excluded from further analysis.

The univariate analysis results are shown in Table 5. Year of publication and methodological quality of the paper correlated positively with quality of outcome reporting. Neither impact factor nor type of journal nor commercial funding was associated with outcome reporting. A multivariate analysis confirmed that both factors (year of publication and methodological quality) were independently associated with outcome reporting (Table 5). Residual plot did not show any evidence of violating assumptions of linear regression.

TABLE 3
Outcome reporting in endometriosis trials: reported pain and fertility outcomes *(continued)*

Outcome domain	Outcome	Trials, n
	Nonmenstrual pelvic pain	6
	Dyschezia	6
	Overall pain	5
	Postoperative pain	3
	Abdominal pain	2
	Back pain	2
	Aggregate pain	1
	Analgesia use	3
	Analgesic requirement	2
	Chest discomfort	1
	General discomfort	1
	General pain	1
	Global intensity of pain	1
	Lateral menstrual pain	1
	Painless first stage of labor	1
	Postoperative opioid analgesia	1
	Rectal pain	1
	Shoulder pain	1
	Thigh pain	1
	Voiding pain	1

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Comment

Summary

In this study, there was outcome reporting heterogeneity. The most common comparable outcome (dysmenorrhea) and measurement tool assessed (visual analog scale from 1 to 10) were reported infrequently.

There was a relationship between the quality of outcomes reported and the quality of a study, but there was not an association with journal impact factor at publication in a multivariable analysis. The RCTs included were from an international setting with different patient populations. This meant we could make no meaningful comparisons relating to ethnicity.

Strengths and weaknesses

The strengths of this review include its originality, robust search strategy, and methodological design. To our knowledge, this is the first systematic review to describe outcome reporting variation in endometriosis trials. To prevent bias in the review process, the search was guided by the Cochrane Collaboration handbook. There was good agreement between reviewers for the selection and assessment of trials, with discrepancies resolved quickly.

This review was not without limitations. We included only RCTs, missing outcomes included in observational studies. Many included trials used outcomes generated from patient-reported questionnaires. These introduce methodological inaccuracies because they lack reliability, are difficult to replicate, and are unable to gauge the sensitivity of the measurement tool.[63] This creates heterogeneity between the endpoints and an inability to compare the effectiveness of an intervention on a specified disease outcome.[64]

Interpretation

The lack of association between journal impact factor and outcome reporting quality may suggest that journals prioritize the results reported or methodological quality ahead of outcome reporting quality. This can introduce outcome reporting bias. The high

TABLE 4
Outcome reporting in endometriosis trials: outcome measures for commonly reported outcomes

Outcome	Outcome measure	n
Dysmenorrhea	Visual analog scale (0–10)	8
	Visual analog scale (0–100)	7
	Visual analog scale (0–10 with description)	3
	Visual analog scale (no description)	1
	Ranked ordinal scale (1–5)	1
	Likert scale (0–10)	3
	Questionnaire (with description)	2
	Questionnaire (ranked symptoms)	1
	Questionnaire (no description)	1
	Number of episodes	1
	Not specified	2
Pregnancy	Serum βHCG	4
	Ultrasound (visualizing fetal heart)	4
	Ultrasound (growth scan)	2
	Not specified	20
Quality of life	World Health Organization Quality of Life-BREF	1
	EuroQol-5D	1
	Short-Form Health Survey 12	1
	Short-Form Health Survey 36	6
	Hospital Anxiety and Depression Scale	2
	Greene Climateric Scale	1
	Blatt Kupperman Menopausal Index	1
	Sabbatsberg Sexual Rating Scale	1
	Revised Sabbatsberg Sexual Rating Scale	2
	Sexual Activity Questionnaire	1

The n indicates the number of the randomized trials reporting on an individual outcome measure.

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prevalence of outcome reporting bias can have an impact on Cochrane reviews.[65] When adjusting for outcome reporting bias, the treatment effect estimate became nonsignificant in 19% of the Cochrane reviews and 26% would have overestimated the treatment effect by 20% or more. Furthermore, it is reported that 85% of research funding is wasted across all aspects of the research cycle, with 3 of the 4 sources of waste closely related to outcome reporting: (1) important outcomes are not assessed, (2) published research fails to set the study in the context with all previous similar research and, (3) greater than 50% of planned study outcomes are not reported.[66]

The All Trials initiative has looked to ensure that all RCTs are published, regardless of their findings. This hopes to eliminate publication bias from studies that are withheld from publication in which there is negative or no effect demonstrated.[67] The selection of cherry-picked attractive results for submission without negative or inconclusive results is difficult to prove or negate without a set of core outcomes.

There is widespread acknowledgment that outcome reporting variation limits the usefulness of research to inform clinical practice.[68] Systematic reviews and metaanalyses are the highest quality research that can be used to implement evidenced-based medicine, yet diversity in outcome reporting prohibits the combination of results for metaanalysis. This is of particular importance to health economists and funding bodies because two thirds of the annual health-related disease costs for endometriosis (€9579) are attributed to loss of productivity. This is comparable with Crohn's disease or diabetes mellitus.[69]

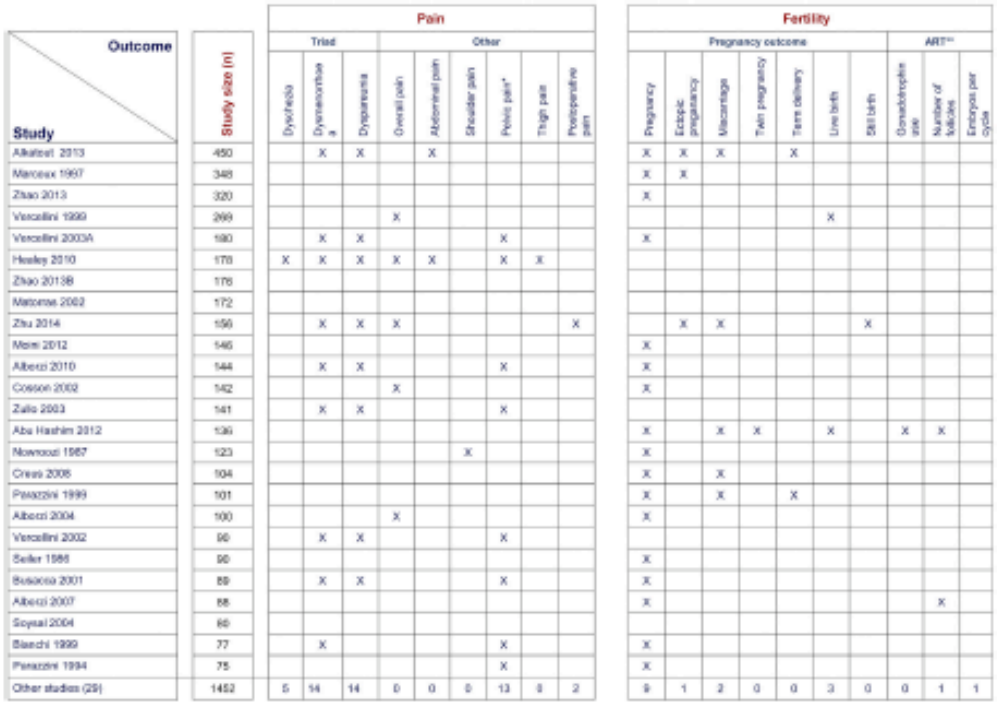
Recommendation(s)

The selection of predefined appropriate outcomes within endometriosis is essential to reduce bias and enhance patient care. The development and use of a collection of well-defined, discriminatory, and feasible outcomes termed a core outcome set would help to address these concerns.[70] These include endpoints to be reported as a minimum while not restricting a particular trial or systematic review to the core outcome set. The Core Outcome Measures in Effectiveness Trials (COMET registration number 691; http://www.comet-initiative.org/studies/details/691) Initiative was launched in January 2010 to address this lack of standardized outcomes through aiding the development of a core outcome set. In most trials, the primary outcome would be selected from the core outcome set.

This move toward higher-quality published research is supported by CoRe Outcomes in WomeN's health (CROWN) Initiative, led by journal editors, encouraging the publication of studies using outcomes from a core outcome set where available.[70] The implementation of core outcome sets will augment the production of comparable data for improved evidence-based patient care.[71] National and international stakeholders including the World Health Organization, the National Institutes of Health, and the Cochrane Collaboration are committed to supporting, developing, and implementing core outcome sets.

This study demonstrates that the reporting of outcomes following the surgical treatment of endometriosis is inconsistent and requires standardization.

FIGURE 2
Outcome reporting in endometriosis trials



Study	Study size (n)	Pain: Triad: Dyschezia	Pain: Triad: Dysmenorrhoea	Pain: Triad: Dyspareunia	Pain: Other: Overall pain	Pain: Other: Abdominal pain	Pain: Other: Shoulder pain	Pain: Other: Pelvic pain*	Pain: Other: Thigh pain	Pain: Other: Postoperative pain	Fertility: Pregnancy outcome: Pregnancy	Fertility: Pregnancy outcome: Ectopic pregnancy	Fertility: Pregnancy outcome: Miscarriage	Fertility: Pregnancy outcome: Twin pregnancy	Fertility: Pregnancy outcome: Term delivery	Fertility: Pregnancy outcome: Live birth	Fertility: Pregnancy outcome: Still birth	Fertility: ART**: Gonadotrophin use	Fertility: ART**: Number of follicles	Fertility: ART**: Embryos per cycle
Alkatout 2013	450		X	X		X					X	X	X		X					
Marcoux 1997	348										X	X								
Zhao 2013	320										X									
Vercellini 1999	269				X											X				
Vercellini 2003A	180		X	X				X			X									
Healey 2010	178	X	X	X	X	X		X	X											
Zhao 2013B	176																			
Matorras 2002	172																			
Zhu 2014	156		X	X	X					X		X	X				X			
Meimi 2012	146										X									
Alborzi 2010	144		X	X				X			X									
Cosson 2002	142				X						X									
Zullo 2003	141		X	X				X												
Abu Hashim 2012	136										X		X	X		X		X	X	
Nowosol 1987	123						X				X									
Crewi 2008	104										X		X							
Pavazzini 1999	101										X		X		X					
Alborzi 2004	100				X						X									
Vercellini 2002	90		X	X				X												
Seller 1986	90										X									
Busacca 2001	89		X	X				X			X									
Alborzi 2007	88										X								X	
Soysal 2004	80																			
Bianchi 1999	77		X					X			X									
Panazzini 1994	75							X			X									
Other studies (29)	1452	5	14	14	0	0	0	13	0	2	9	1	2	0	0	3	0	0	1	1

*Pelvic pain = This includes non-menstrual pelvic pain **ART = Assisted reproductive technology

Outcome reporting in endometriosis trials shows the largest 25 studies listed by study size showing pain and fertility outcomes.

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There is no internationally agreed selection of outcomes for trials and systematic reviews evaluating surgical interventions for the treatment of endometriosis. The International Collaboration to Harmonize Outcomes and Measures for Endometriosis (iHOME www.blizard.qmul.ac.uk/research-project/1335-iHOME.html) has been established to address these barriers to improved patient care. iHOME aims to develop and implement the use of a core outcome set in the treatment of endometriosis. This will improve the possibility of scientifically summarizing outcomes from different studies and centers and also reduce outcome reporting bias.[65]

In the current absence of a core outcome set for endometriosis, we

TABLE 5
Outcome reporting in Endometriosis trials: Multiple linear regression analyses to determine factors associated with quality of outcome reporting

	Univariable		Multivariable[a]	
Factor	Rho Spearman	*P* value	β	*P* value
Study quality[b]	0.379	.010	0.325	.038
Impact factor at publication	0.190	.212	—	—
Journal type (specialist/generalist)[c]	—	.691	—	—
Year of publication	0.294	.050	0.057	.040
Commercial funding[c]	—	.370		—

[a] Based on best subset regression; [b] Measurement details in *Materials and Methods*; [c] Based on Mann-Whitney *U* test.

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recommend the use of the 3 most common outcomes and their measures within the domains of pain (dysmenorrhea, dyspareunia, and pelvic pain) and subfertility (pregnancy, miscarriage, and live birth) to maximize the contribution to a metaanalysis following trial completion (Tables 3 and 4).

Conclusion

The variation in outcomes leads to multidirectional research that lacks comparabilityand threatens patient care. There is an evident need for harmonization toward patient-centered clinical outcomes through the development of a core outcome set in endometriosis. ■

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APPENDIX

Search strategy: Medline

n	Database		Citations (n)
1	Medline	Exp endometriosis/	17697
2	Medline	Endometrio*.ti,ab	22651
3	Medline	1 or 2	26105
4	Medline	3 [limit to: (document type: randomized controlled trial)]	464

Hirsch. Outcome reporting in endometriosis trials. Am J Obstet Gynecol 2016.

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Systematic review

Diagnostic accuracy of cancer antigen 125 for endometriosis: a systematic review and meta-analysis

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Background The development of a non-invasive and accurate diagnostic biomarker for endometriosis is urgently needed.

Objective Evaluate the diagnostic accuracy of serum cancer antigen 125 (CA 125) for endometriosis.

Search strategy We searched EMBASE, MEDLINE, and Web of Science from inception to January 2016.

Selection criteria Diagnostic accuracy studies of serum CA 125 (index test) for histologically confirmed endometriosis (reference standard) were included.

Data collection and analysis Two authors independently selected trials, extracted study characteristics and data. Methodological quality was assessed using Quality Assessment of Comparative Diagnostic Accuracy Studies (QUADAS-2) checklist.

Main results Twenty-two studies (16 cohort, six case-control), 3626 participants, were identified. Bivariate hierarchical models were used to pool accuracy data of 14 studies (2920 participants) using CA 125 ≥ 30 units/ml. Pooled specificity was 93% (95% CI 89–95%) and sensitivity 52% (95% CI 38–66%). CA 125 was significantly more sensitive for the diagnosis of moderate or severe endometriosis compared with minimal disease (63%, 95% CI 47–77% versus 24%, 95%CI 19–32%, *P*-value = 0.001).

Conclusions CA 125 performs well as a rule-in test facilitating expedited diagnosis and ensuring investigation and treatment can be confidently tailored for the management of endometriosis. Unfortunately, a negative test, CA 125 < 30 units/ml, is unable to rule out endometriosis.

Keywords Biomarkers, cancer antigen 125, endometriosis, non-invasive diagnosis.

Tweetable abstract Blood test CA 125: a rule-in test for the diagnosis of women presenting with symptoms of endometriosis

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Introduction

Endometriosis, defined as the presence of endometrial glands and stroma located outside the uterus is characterised by pain and subfertility. Estimates of disease prevalence suggest endometriosis affects up to 75% of symptomatic women yet is commonly under-diagnosed. The gold standard diagnostic test is histological diagnosis. The invasive nature of diagnosis accounts for a significant delay in a formal diagnosis. This delay could result in disease progression, symptom deterioration and an annual societal cost of US$49.6 billion in the USA.[1] Evaluation of non-invasive diagnostic biomarkers has not identified an accurate test for the detection of endometriosis.[2,3] A rule-in test could reduce time to diagnosis, provide psychological support, and provide reassurance to the clinician to offer tailored treatment options.[4]

Cancer antigen 125 (CA 125), a well-established marker for epithelial cell ovarian cancer, is derived from coelomic epithelia including the endometrium, fallopian tube, ovary, and peritoneum.[5] CA 125 is raised in endometriosis through stimulation of coelomic epithelia[6] and is the most

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investigated non-invasive diagnosis marker. Individual studies have methodological limitations in patient selection,[7,9,13–21] poor conduct of the index test,[7–12,21–31] and poor conduct of the reference test.[17–20,32–57] Two diagnostic reviews exist; however, the first is over 15 years old and includes studies with high risk of verification bias[58] and the second is of poor methodological quality.[59]

We conducted a meta-analysis to assess the diagnostic accuracy of CA 125 for histologically confirmed endometriosis.

Methods

A protocol with explicitly defined objectives, criteria for study selection, approaches to assessing study quality, and statistical methods was developed and prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO), registration number CRD42015017630, available online www.crd.york.ac.uk/prospero. We have reported the systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[60]

A comprehensive and systematic literature review was undertaken searching EMBASE, MEDLINE, and Web of Science from inception to January 2016. We searched the register using MeSH and free text combinations with Boolean logic of the following search terms: endometrio*, test*, diagnos*, accura*, marker, screen*, detect*, CA 125, Cancer Antigen 125, CA-125, CA125. There were no language or date restrictions (Supporting Information Appendix S1).

Two reviewers (M.H. and J.M.D.) independently screened titles and abstracts. They critically reviewed the full text of selective studies to assess eligibility. Any discrepancies between the reviewers were resolved by discussion. We included prospective and retrospective observational studies (cohort and case–control) assessing the diagnostic accuracy of pre-operative serum CA 125 to detect endometriosis confirmed by histology collected at robotic, laparoscopic or open surgery. We excluded studies that used visual confirmation of endometriosis as the reference standard, studies that only assessed ovarian cysts, and those where the comparator group included malignant disease.

Two reviewers (M.H. and J.M.D.) extracted the data independently using a pilot-tested data extraction sheet. Information collected from each study included study design, setting, and participants. We extracted all relevant raw data from each study. Two reviewers (M.H. and J.M.D.) independently assessed each study's methodological quality using the Quality Assessment of Comparative Diagnostic Accuracy Studies (QUADAS-2) checklist: patient selection, conduct of the index test, conduct of the reference test, and patient flow. We considered studies to be of high quality if they sampled an appropriate patient spectrum, used consecutive recruitment, index test was performed before the reference standard, and all participants underwent the same reference standard.[61] The following were considered study qualities with potential to introduce bias: patients with a pre-operative ultrasound diagnosis of endometriosis, case-control studies, control groups that did not undergo the reference standard test, and studies with <85% histological confirmation of endometriosis. These were assessed with subgroup and sensitivity analysis.

Data was extracted for the number of true positives, true negatives, false positives, and false negatives for the index test at the documented threshold. Where data were unavailable, the authors used the published sensitivities and specificities to calculate these data necessary to complete a 2×2 table. We actively contacted authors to seek clarification and requested missing data or additional data to complete our analysis.[7,31,62,63] Discrepancies between the reviewers (M.H. and J.M.D.) were resolved through discussion, by contacting the authors, or by consultation with a third reviewer (K.K.).

Data synthesis was performed using *a priori* hypothesis described in the protocol. Where studies reported multiple cut-off values for CA 125 we selected the closest value to the laboratory upper limit of normality (35 units/ml) for our analysis.[64] We explored variation in accuracy indices graphically using Forest plots of sensitivity and specificity and ROC plane plots of sensitivity against specificity. As the studies used different cut-offs, we grouped them in order to isolate subsets of studies using the same cut-off. In the case of no evidence of threshold effect within these subsets of studies, we fitted hierarchical bivariate random effects model[65] and obtained the following summary accuracy measures with corresponding 95% confidence intervals: sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio. Post-test probabilities were calculated based on pooled estimates of likelihood ratios and overall pretest odds based on published prevalence studies of endometriosis by clinical symptoms or signs. In case of evidence of threshold effects we summarised the analyses with the summary receiver operating characteristics curve. To investigate sources of heterogeneity, we performed subgroup analysis on the following pre-specified groups: (1) comparison of study design (cohort versus case-control), (2) comparison of positive ultrasound findings for endometriosis (ovarian cyst versus no cyst or no ultrasound), (3) comparison of revised American Fertility Score[66,67] (disease stage 1–2 versus 3–4). Sensitivity analyses were performed to evaluate the impact on accuracy of excluding studies that had elements of verification bias, including 87% histological confirmation of endometriosis[11] and controls that did not undergo the reference standard.[9] We checked differences in sensitivity and specificity

between subgroups by adding covariates to the bivariate model. STATA software was used for statistical analyses. (StataCorp 2013; Release 13).

Results

Twenty-two studies included 3626 participants (Figure 1).[7–13,21–31,62,68–70] Nineteen prospective observational studies[7,8,10,12,13,22–31,62,68–70] and three retrospective observational studies[9,11,21] were included for analysis. Two studies did not include analysable data and the authors could not be contacted.[7,62] The studies were relatively small (<300 participants), with the exception of Kitawaki et al.,[8] Cho et al.,[9] Yang et al.,[21] and Santulli et al.[31] (Table 1). All studies were conducted in high-resource settings.[71] Fifteen studies recruited patients from infertility clinics[7,10–13,22–24,26,27,29,31,62,68,70] and eight studies included recruited patients from general gynaecology clinic or elective gynaecological theatre sessions.[8,10,12,21,23,26,29,31] Twelve studies reported including patients with pain symptoms.[8,12,13,22–24,26,29–31,62,70] Twelve studies recruited patients with pre-operative imaging available indicating an ovarian cyst.[8–10,12,13,23,25,26,28,31,62,70] Endometriosis was confirmed by histology collected at either laparoscopic,[10,11,13,21–24,27–31,62,67,70] laparoscopy or laparotomic,[7,8,12,26,68] or did not specify the route of surgery.[9,25] The staging of endometriosis was classified using the revised American Fertility Society classification 1985[66] or the revised American Fertility Society classification 1997.[67] Nine studies (954 participants) included participants with minimal to mild endometriosis[7,9,10,12,13,26,27,62,68] and 14 studies (1479 participants) included participants with moderate to severe endometriosis.[7,9,10,12,13,21,24,26–28,30,62,68,69]

The authors' judgment on risk of bias was used with the revised assessment tool QUADAS2 (Quality assessment of comparative diagnostic accuracy studies) (Supporting Information Figure S1). Seventeen of the 22 studies had a low risk of bias owing to patient timing and flow. Two

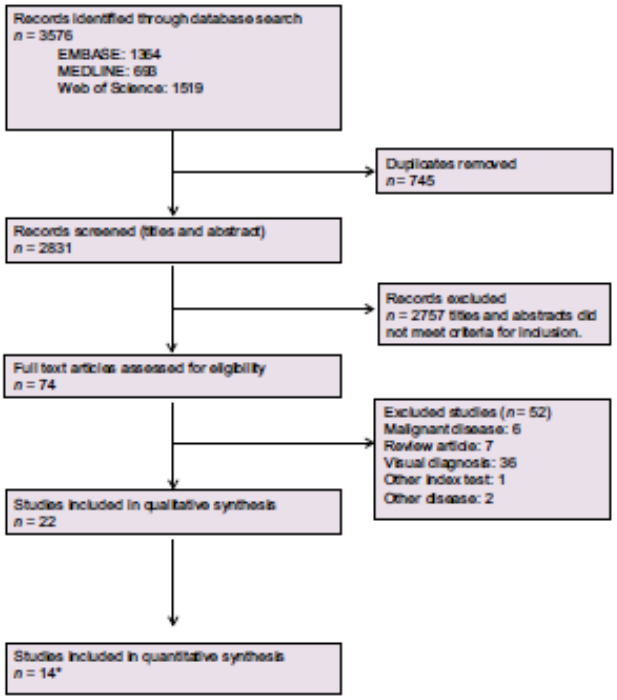

Figure 1. Flow of included studies. *Eight studies with a CA 125 cut-off value <30 units/ml were not meta-analysed due to statistical variation with evidence of a threshold effect limiting accuracy estimates.

Table 1. Characteristics of included studies

Author	Year	Country	Participants	Study design	Participant characteristics	Ovarian cysts included	Endometriosis staging criteria
Wild	1991	USA	93	Cohort	Infertility	No	RAFS 1985
Adamyan	1993	USSR	49	Case-control	Cysts	Yes	RAFS 1985
Mdio	1994	USA	35	Cohort	Infertility	No	RAFS 1985
Abrao	1997	Brazil	50	Case-control	Not specified/tubal reanastomosis	Yes	rAFS 1985
Chen	1998	Taiwan	99	Cohort	Pain	No	rAFS 1985
Kitawaki	2005	Japan	350	Cohort	Gynaecology referral/pain/cysts	Yes	rAFS 1997
Amaral	2006	Brazil	52	Cohort	Infertility/pain/tubal ligation	No	rAFS 1997
Cho	2008	South Korea	760	Case - control	Elective gynaecological surgery/cysts	Yes	rAFS 1997
Gajbhiye	2008	India	77	Cohort	Infertility department/cysts	Yes	rAFS 1997
Jing	2008	Japan	61	Case - control	Pain/infertility/cysts	Yes	rAFS 1997
Salahpour	2009	Iran	60	Cohort	Pain/infertility/miscarriage	No	rAFS 1997
Kurdoglu	2009	Turkey	127	Cohort	Pain/infertility/general gynaecology/cysts	Yes	rAFS 1997
Florio	2009	Italy	99	Cohort	Endometrioma vs other cysts	Yes	rAFS 1997
Tokmak	2011	Turkey	88	Cohort	Cysts	Yes	rAFS 1997
Vodolazkaia	2012	Belgium	296	Cohort	Infertility/biobank	No	rAFS 1997
Ramos	2012	Brazil	104	Cohort	Pain/infertility/tubal ligation/cysts	Yes	rAFS 1997
Mohammed	2013	Egypt	60	Cohort	Pain/infertility	No	rAFS 1997
Sayan	2013	Turkey	100	Cohort	Pain/infertility/general gynaecology/ tubal ligation/cysts	Yes	rAFS 1997
Kubatova	2013	Turkey	73	Cohort	Pain/infertility/cysts	Yes	rAFS 1997
Bilibio	2014	Brazil	97	Case - control	Pain/infertility/tubal ligation	No	rAFS 1997
Santulli	2015	France	685	Cohort	Pain/infertility/tubal surgery/cysts	Yes	rAFS 1997
Yang	2015	China	309	Case-control	Elective gynaecological surgery	Yes	rAFS 1997

studies[9,21] were described as high risk of bias as the asymptomatic control group did not undergo surgery. All studies had a low risk of bias attributed to the reference standard, as this was deemed an objective histological assessment. One study was aware of the index test result prior to the reference standard,[21] one study performed the index test following the reference standard,[7] and a further study analysed the index test after the reference standard.[11] These were deemed high risk of bias for conduct of the index test. Fourteen studies had a low risk of bias owing to patient selection, six were high risk owing to case-control design,[7,9,13,21,23,25] and the remaining two were unclear.[11,12] Regarding applicability concerns, all studies were low risk for the index and reference standard. Twelve studies were low risk for patient selection and ten studies unclear owing to case-control design and inclusion of patients for tubal surgery, a group who may not be screened routinely for endometriosis.[7–10,13,21,26,29,31,62]

Forest plots illustrate the variation in sensitivity and specificity between individual studies for the detection of pelvic endometriosis with serum CA 125 measurement (Supporting Information Figure S2). Individual study sensitivities ranged from 0%[27] to 87%[30] and specificity from 51%[11] to 100%.[70]

Fourteen studies, 2920 participants (1584 with endometriosis, 1336 controls) were meta-analysed to assess the accuracy of CA 125 $\geq$ 30 units/ml for the presence of endometriosis.[8–10,12,13,21,24–27,30,39,69,70] Serum CA 125 $\geq$ 30 units/ml had a pooled sensitivity of 52.4% (95% CI 37.9–66.4%) and specificity 92.7% (95% CI 89.4– 95.1%) with no apparent correlation between sensitivity and specificity (Figure 2). A sensitivity analysis excluding an outlier study with 0% sensitivity[27] did not significantly alter results (data not shown). When a mix of cut-off points for CA 125 were included into the analyses, a high variation in both sensitivity and specificity was observed with a clear threshold effect, making accuracy estimates for this subgroup less useful (Figure 2).

Sources of heterogeneity were highlighted as study design (case-control versus cohort), the pre-operative ultrasound

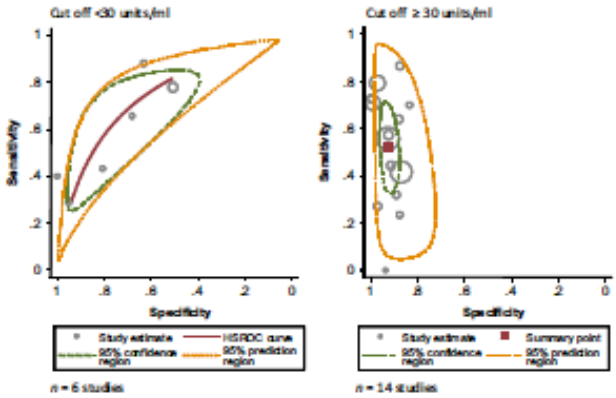

Figure 2. Summary of Receiver Operating Characteristic Curves (CA 125 ≥ 30 or <30 units/ml).

diagnosis of ovarian cysts and disease stage (Supporting Information Table S1). CA 125 showed higher sensitivity with increasing disease severity, 24.8% (95% CI 18.8–32.1%; stage I–II) versus 63.1% (95% CI 47.2–76.5%; stage III–IV). There were no significant differences in pooled sensitivity and specificity for the detection of endometriosis in the presence or absence of ovarian cysts or change in study design.

Sensitivity analyses excluding studies with verification limitations[9,11] did not change accuracy estimates of CA 125 for detecting the presence of endometriosis (Table 2).

Discussion

Main findings

CA 125 performs well as a rule-in test, facilitating expedited diagnosis and ensuring investigation and treatment can be confidently tailored for the management of endometriosis. Unfortunately, a negative test, CA 125 < 30 units/ml, is unable to rule out endometriosis.

Strengths and limitations

This is the first prospectively registered review. We conducted a comprehensive search strategy, robust methodology, and statistical analysis. Previously published systematic reviews, are out of date[58] or associated with methodological bias arising from case-control studies[59] and verification bias arising from the reliance upon visual inspection, which is now known to be inaccurate.[72] All studies included in this study reported the primary endpoint using the reference standard of histologically confirmed endometriosis.

Diagnostic reviews are not without limitations. There was wide variation observed in the sensitivity of CA 125 between individual studies. This is thought to be due to clinical

Table 2. Sensitivity analyses

	Studies	Endometriosis diagnosed/ controls	Sensitivity (95% CI)	Specificity (95% CI)	LR^+ (95% CI)	LR^- (95% CI)	DOR (95% CI)
Cut-off level ≥30							
Total	14	1584/1336	52.4 (37.9–66.4)	92.7 (89.4–95.1)	7.2 (4.2–12.3)	0.5 (0.4–0.7)	14.0 (6.3–31.4)
Sensitivity analysis*	13	1353/807	51.8 (36.0–67.3)	93.0 (89.0–95.6)	7.4 (4.0–13.5)	0.5 (0.4–0.7)	14.2 (5.8–34.7)
Cut-off level <30							
Total	6	331/221	58.1 (39.7–74.5)	79.4 (60.1–90.8)	2.8 (1.6–4.8)	0.5 (0.4–0.7)	5.3 (3–9.5)
Sensitivity analysis**	5	214/140	54.6 (33.6–74.2)	88.2 (67.8–92.1)	3.3 (2.0–5.4)	0.5 (0.4–0.8)	6 (3.1–11.3)

*Without Cho et al.[9]
**Without Vodolazkaia et al.[11]

heterogeneity, for example Mohamed et al.[24] and Yang et al.[21] evaluated a population of women with advanced endometriosis, whereas Molo et al. and Wild et al. recruited purely from a fertility clinic setting. Several other gynaecological diseases cause a rise in CA 125 including, ovarian epithelial carcinoma, leiomyoma, and pelvic inflammatory disease and often, included studies did not adequately rule these conditions out. There was variation in CA 125 assay assessment, which could introduce bias. We included case-control studies,[7,9,13,21,23,25] which can have large discrepancies between the anticipated prevalence of the groups.

Interpretation

CA 125 performs well as a rule-in test. This offers women, presenting for the first time with pain or infertility and a positive test, the confidence that an initial diagnosis is correct. This may decrease delays in the diagnostic pathway, allowing women relief, liberation and legitimisation of their symptoms, together with access to support and an opportunity to discuss tailored medical or surgical management.[4]

To minimise the false negative rate, the use of CA125 is limited to women with symptoms of endometriosis, where there is a high suspicion of disease and a high prevalence of disease within the population. The indiscriminate use of CA 125 should be avoided in favour of a targeted rule-in test for symptomatic women and their clinicians wishing for further confidence in diagnosis, prior to delivering a therapeutic intervention. CA 125 performs poorly as a rule-out test and 49% of those with endometriosis will have a negative test. This can cause uncertainty and confusion among those with a negative test, potentially leading to unnecessary presumptive hormonal treatment. Alternative non-invasive biomarkers currently being investigated include human epididymis protein 4[73] and miRNA,[74] which provide potential for accurate biomarkers of the future. It is therefore unlikely that CA 125 will have a lasting role as a non-invasive diagnostic tool for endometriosis. However, there is currently no validated, accurate test available with sensitivity >75% and specificity >75%.[2,3] In the absence of a more accurate non-invasive test for the diagnosis of endometriosis, we recommend the use CA 125 > 30 units/ml as a rule-in test amongst symptomatic women with a negative ultrasound.

Conclusions

In symptomatic women, the use of CA 125 ≥ 30 units/ml is highly specific for diagnosing endometriosis. This specific test can, when positive, provide earlier access to treatment options, and reduce time to diagnosis and anxiety among endometriosis sufferers. A CA 125 of <30 units/ml does not exclude endometriosis and further investigation is required. We recommend further research on alternative biomarkers that are both sensitive and specific for the diagnosis of endometriosis.

Disclosure of interests

Full disclosure of interests available to view online as supporting information.

Contribution to authorship

MH, JMND, KSK & CJD developed the concept and design of the study. MH & JMND undertook data acquisition. MNP performed data analysis and interpretation. All authors were involved with drafting the article and final approval and agree to be responsible for its accuracy.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Search Strategy.

Table S1. Sub-group analysis.

Figure S1. Quality Assessment using QUADAS2 Assessment tool.

Figure S2. Forest plots of sensitivity and specificity in descending order of sensitivity, stratified by cut-off (CA 125 ≥ 30 or <30 units/ml). ■

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Googling endometriosis: a systematic review of information available on the Internet

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BACKGROUND: The demand for health information online is increasing rapidly without clear governance.

OBJECTIVE: We aim to evaluate the credibility, quality, readability, and accuracy of online patient information concerning endometriosis.

STUDY DESIGN: We searched 5 popular Internet search engines: aol.com, ask.com, bing.com, google.com, and yahoo.com. We developed a search strategy in consultation with patients with endometriosis, to identify relevant World Wide Web pages. Pages containing information related to endometriosis for women with endometriosis or the public were eligible. Two independent authors screened the search results. World Wide Web pages were evaluated using validated instruments across 3 of the 4 following domains: (1) credibility (White Paper instrument; range 0-10); (2) quality (DISCERN instrument; range 0-85); and (3) readability (Flesch-Kincaid instrument; range 0-100); and (4) accuracy (assessed by a prioritized criteria developed in consultation with health care professionals, researchers, and women with endometriosis based on the European Society of Human Reproduction and Embryology guidelines [range 0-30]). We summarized these data in diagrams, tables, and narratively.

RESULTS: We identified 750 World Wide Web pages, of which 54 were included. Over a third of Web pages did not attribute authorship and almost half the included pages did not report the sources of information or academic references. No World Wide Web page provided information assessed as being written in plain English. A minority of web pages were assessed as high quality. A single World Wide Web page provided accurate information: evidentlycochrane.net. Available information was, in general, skewed toward the diagnosis of endometriosis. There were 16 credible World Wide Web pages, however the content limitations were infrequently discussed. No World Wide Web page scored highly across all 4 domains.

CONCLUSION: In the unlikely event that a World Wide Web page reports high-quality, accurate, and credible health information it is typically challenging for a lay audience to comprehend. Health care professionals, and the wider community, should inform women with endometriosis of the risk of outdated, inaccurate, or even dangerous information online. The implementation of an information standard will incentivize providers of online information to establish and adhere to codes of conduct.

Key words: accuracy, credibility, endometriosis, online information, patients, quality, readability, systematic review

Introduction

Endometriosis is benign gynecological disease that affects 1 in 10 women of reproductive age. It is characterized by pain and subfertility with associated reduced quality of life.[1] The economic burden of endometriosis is of a similar magnitude to other chronic diseases such as diabetes.[2] There is a paucity of high-quality research to guide clinical practice; this leads to unwarranted and unjustified variations in patient care.[3]

The Internet is the source of health information, as patients can access health information quickly, conveniently, and privately. There are an estimated 6.75 million health searches daily in Google representing 4.5% of all searches performed.[4] There has been rapid growth in the number of World Wide Web pages providing health information with little or no governance.[5] Seven in 10 adults regularly search for an explanation and information on a new diagnosis or treatment.[6-8] Information provided is commonly written at a high literacy level, compounding the difficulties for patients untrained in establishing whether the information is accurate. Exposure to complex, ungoverned, unfounded health information that lacks expert editorial supervision could negatively affect patient understanding, compliance, and decision making. This could lead to poorer health outcomes, including harm.[9-13] There are no systematic reviews assessing the quality of online patient information pertaining to endometriosis.

We systematically assessed the accuracy, quality, readability, and credibility of World Wide Web pages providing women with endometriosis and the public information regarding the diagnosis and management of endometriosis.

Materials and Methods

Sources

A protocol with explicitly defined objectives, criteria for World Wide Web

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page selection, and approaches assessing outcome selection was developed and registered with the International Prospective Register of Systematic Reviews, identification number: CRD42016036134. This review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement.[14]

World Wide Web page selection

We developed a comprehensive search strategy in consultation with health care professionals, researchers, and women with endometriosis. We used a key word analytic instrument (www.semrush.com) to inform our selection of search terms, which provides analytical information related to search terms. We are confident we identified and selected search terms commonly used by women with endometriosis. We used the following search terms: (1) "endometriosis," 4,560,000 searches per annum; (2) "endometriosis symptoms," 325,200 searches per annum; (3) "endometriosis treatment," 64,800 searches per annum; (4) "endometriosis pain," 19,200 searches per annum; and (5) "endometriosis diagnosis," 15,600 searches per annum. During March 2016, we searched five popular search engines: aol.com, ask.com, bing.com, google.com, and yahoo.com.

Individuals rarely examine more than the first 3 pages of a search.[11] We therefore extracted the World Wide Web pages from the first 3 pages for each search term within each search engine. Location services were disabled to eliminate geographical bias.

We organized the extracted World Wide Web pages and removed duplicates. Two reviewers (M.H. and S.A.) independently screened the full content of World Wide Web pages to assess eligibility. All data extraction was performed using piloted data extraction instruments. We pilot tested each instrument using a representative sample of the World Wide Web pages to be reviewed. This testing helped identify data missing from the form, or likely to be superfluous. This allows authors trialing the form to provide feedback that certain coding instructions are confusing or incomplete (eg, a list of options may not cover all situations). Any discrepancies between the reviewers were resolved by discussion with a consensus required before the form is modified to avoid any misunderstandings or later disagreements. We repeated the pilot testing on a new set of World Wide Web pages where no major changes were needed.[15]

We included World Wide Web pages providing health information about endometriosis >300 words in length on the initial page following click through from the search engine. We excluded World Wide Web pages for the following reasons; (1) non-English language; (2) inaccessible, for example password restricted; (3) aimed at a professional audience, for example scientific publication; (4) excessive commercial advertising (≥2 commercial advertisements); and (5) content related solely to the lived experience of endometriosis, for example a patient's diary or blog.

Those World Wide Web pages that met the criteria for inclusion were saved as a portable document format for evaluation and data extraction by 2 independent authors (M.H. and S.A.). M.H. and J.M.D. did not assess any World Wide Web pages to which they had previously contributed.

World Wide Web pages characteristics

Two reviewers (M.H. and S.A.) extracted the World Wide Web page characteristics independently using a piloted data extraction sheet. Information extracted from each World Wide Web page included country of origin, disease-specific information, listed authors, and privacy statements. Two reviewers (M.H. and S.A.) independently assessed each World Wide Web page using validated instruments including assessments of: (1) credibility assessed using the White instrument[16] anchored between 0 (poor) and 10 (excellent); (2) quality assessed using the DISCERN[17] instrument anchored between 0 (poor) and 85 (excellent); and (3) readability assessed using the Flesch-Kincaid[18] instrument anchored between 0 (poor) and 100 (excellent). Discrepancies were resolved by discussion.

Quality assessment

Two reviewers (M.H. and S.A.) underwent training in the use of the quality assessment instruments. We assessed accuracy using a prioritized list of recommendations included within the European Society of Human Reproduction and Embryology (ESHRE) endometriosis guidelines.[19] The ESHRE guideline was selected for comparison as this was objectively assessed to represent the highest quality endometriosis guideline.[20] All recommendations were extracted by 2 authors independently. Discrepancies were resolved by discussion. In consultation with health care professionals, researchers, and women with endometriosis, the recommendations were scored as: (1) critical for decision making, (2) important but not critical for decision making, and (3) not critical and not important for decision making. Fifteen guideline recommendations were selected as statements critical for decision making (appendix). The assessment of accuracy was standardized against selected guideline recommendations. This approach has been utilized in similar research studies.[21]

Two reviewers (M.H. and S.A.) independently reviewed each World Wide Web page assessing the accuracy of information. Each recommendation was scored: 0 (if absent or incorrectly described), 1 (present and incompletely described), or 2 (present and completely described). Accuracy assessment was anchored between 0 and 30. Discrepancies were resolved by discussion. We classified World Wide Web pages with a score ≥20 as accurate.

The World Wide Web page's credibility was assessed by 2 reviewers independently using the validated White instrument.[16] This instrument, designed for consumers of health information, provides a set of criteria that can be used to accurately and reliably assess the quality of health information on the Internet. Credibility was assessed using 10-point criteria: (1) source; (2) context; (3) currency; (4) utility; (5) editorial review process; (6) hierarchy of evidence; (7) statement of original source; (8) disclaimer, which included

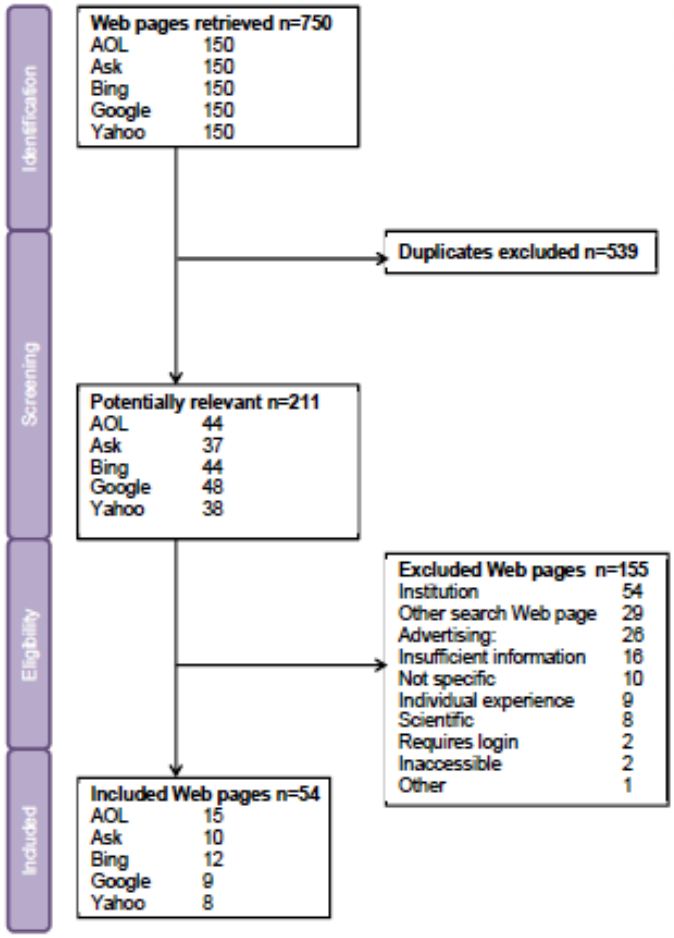
ownership, sponsorship, funding, and advertising; (9) omissions; and (10) feedback. Each criterion was scored 0 (absent) or 1 (present) giving a score anchored between 0-10.[22] Discrepancies were resolved by discussion. We classified those World Wide Web pages with a score ≥7 as credible.

The World Wide Web page's quality was assessed by 2 reviewers independently using a validated instrument, DISCERN,[17] designed to assess the quality of written information on treatment choices that can be applied to any disease.[7,17] The DISCERN instrument offers a framework for the production, evaluation, and screening of written consumer health information. This includes 16 questions assessed using a Likert scale anchored between 1 (do not agree) and 5 (agree).[17] Discrepancies were resolved by discussion. We classified those World Wide Web pages as high (>53), moderate (27-52), and low (<27) quality.

The World Wide Web page's readability was assessed using the Flesch-Kincaid reading-ease test.[18] This formula presents a score as a US grade level, making it easier for teachers, parents, librarians, and consumers of health information to judge the readability level of various texts. The Flesch-Kincaid score is generated from the following equation: 206.835 − 1.015 (total words/total sentences) − 84.6 (total syllables/total words) (www.readability-score.com).[18] The scores were anchored between 0 (complex language) and 100 (simple language) and could be categorized by reading age or educational status: 90-100 (5th grade); 80-90 (6th grade); 70-80 (7th grade); 60-70 (8th and 9th grade); 50-60 (10th, 11th, and 12th grade); 30-50 (college); or 0-30 (college graduate). Discrepancies were resolved by discussion.

A large-scale national assessment of the average US reading level performed by the National Center for Education Statistics found that the typical US citizen reads between a 7th and 8th grade level.[23] It is recommended that online health information should not exceed the level of US 7th grade writing and reading.[24] We therefore expected World Wide Web pages to have a readability score level of US education ≤7th grade (>70) to be deemed appropriate for a patient and public audience.

FIGURE
Flow of included Web pages



Flow of included World Wide Web pages.
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Analysis

The World Wide Web page characteristics and assessments were summarized in tabular form and presented with descriptive statistics within summary tables and diagrams.

Results

The search strategy identified 750 World Wide Web pages assessed for eligibility. We screened 211 World Wide Web pages following the exclusion of 539 duplicate sites. Two authors independently applied an inclusion and exclusion criteria when screening the pages. We included 54 World Wide Web pages in our final assessment (Figure and Table).

TABLE 1
World Wide Web page characteristics and summary of quality, accuracy, credibility, and readability assessment

ID	Web domain	Country	Listed authors	Privacy statement	Quality[a]	Accuracy[b]	Credibility[c]	Readability[d]
1	endocenter.org	United States	No	Yes	46	6	7	26.8
2	endometriosis.org	Global	No	Yes	62	10	8	30.7
3	endometriosis.org	Global	No	Yes	50	12	6	39
4	endometriosis.org	Global	No	Yes	50	½	8	38.3
5	endometriosis.org	Global	Yes	Yes	37	1	4	47.6
6	endometriosis.org	Global	No	Yes	42	7	5	38.5
7	home.bt.com	United Kingdom	Yes	Yes	46	5	5	38.2
8	lifestyle.one	United Kingdom	Yes	No	48	4	5	52.3
9	medical-dictionary.thefreedictionary.com	United States	No	Yes	62	10	8	24.3
10	metro.co.uk	United Kingdom	Yes	No	37	2	3	61
11	pain.about.com	United States	Yes	Yes	61	13	6	45.9
12	patient.info	United Kingdom	Yes	No	69	10	9	48.1
13	shetrust.org.uk	United Kingdom	No	No	35	2	4	23
14	sogc.org	Canada	No	Yes	42	9	4	33.7
15	womenshealth.about.com	United States	Yes	Yes	42	2	6	32.6
16	activebeat.com	Canada	No	Yes	28	1	3	34.8
17	babycentre.co.uk	Global	No	Yes	40	10	8	55.4
18	channel4embarrassingillnesses.com	United Kingdom	No	Yes	32	2	5	49.8
19	cwhn.ca/node/40781	Canada	No	No	43	4	3	38.5
20	endo-resolved.com	United Kingdom	No	No	35	3	4	38.3
21	endo-resolved.com	United Kingdom	No	No	37	2	4	32.2
22	endo-resolved.com	United Kingdom	No	No	54	5	4	47.3
23	endometriosis.ie	Ireland	No	Yes	39	10	4	23.5
24	endometriosisaustralia.org	Australia	No	No	58	10	5	49.1
25	endometriosisinstitute.com	United States	No	No	50	8	4	23
26	endometriosisinstitute.com	United States	No	No	51	8	4	21.3
27	evidentlycochrane.net	United Kingdom	Yes	No	45	4	7	29.6
28	evidentlycochrane.net	United Kingdom	Yes	No	56	2	7	40.4
29	healthline.com	United States	Yes	Yes	62	7	8	40.6
30	hellomagazine.com	United Kingdom	No	Yes	38	3	4	51.7
31	independent.co.uk	United Kingdom	Yes	Yes	32	4	5	46.3
32	livescience.com	Global	Yes	Yes	47	6	3	34.9
33	medicalnewstoday.com	United Kingdom	Yes	Yes	45	2	8	24.8
34	netmums.com	United Kingdom	No	No	45	5	4	28.1
35	nytimes.com	United States	Yes	Yes	51	5	8	57
36	nzendo.org.nz	New Zealand	No	No	40	6	4	34.2
37	pelvicpain.org.uk	United Kingdom	No	Yes	57	11	8	21.5
38	pelvicpain.org.uk	United Kingdom	No	Yes	38	6	5	33.6

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TABLE 1
World Wide Web page characteristics and summary of quality, accuracy, credibility, and readability assessment
(continued)

ID	Web domain	Country	Listed authors	Privacy statement	Quality[a]	Accuracy[b]	Credibility[c]	Readability[d]
39	prevention.com	United States	Yes	Yes	35	3	4	32.8
40	students4bestevidence.net	United Kingdom	Yes	Yes	47	28	7	5
41	theguardian.com	United Kingdom	Yes	Yes	40	6	3	56.8
42	theguardian.com	United Kingdom	Yes	Yes	31	5	4	53.4
43	uptodate.com	United Kingdom	Yes	Yes	64	13	9	33.8
44	womens-health.co.uk	New Zealand	No	Yes	22	3	3	38.1
45	womens-health.co.uk	New Zealand	No	Yes	35	5	2	49.3
46	youngwomenshealth.org	United States	Yes	No	61	4	4	55.1
47	en.wikipedia.org	Global	No	Yes	50	11	8	23.9
48	healthfacty.com	Canada	Yes	Yes	32	1	5	44.9
49	betterhealth.vic.gov.au	Australia	No	Yes	61	8	7	30.8
50	endometriosis-uk.org	United Kingdom	No	Yes	42	2	5	31
51	endometriosis-uk.org	United Kingdom	No	Yes	40	1	5	24.8
52	endometriosis-uk.org	United Kingdom	No	Yes	41	2	5	32
53	endometriosis-uk.org	United Kingdom	No	Yes	53	0	5	51.6
54	endometriosis-uk.org	United Kingdom	No	Yes	33	2	5	48.3
Median IQR					44 (37–51)	5 (4–7)	5 (2–9)	38.2 (30–48)

IQR, Interquartile range.

[a] DISCERN tool to assess quality of information (range 16–80); [b] Accuracy assessed using selected criteria from 2013 European Society of Human Reproduction and Embryology guidelines (range 0–30); [c] Credibility based on 10 criteria (range 0–10); [d] Readability assessed using Flesch-Kincaid reading-ease tool (range 0–100).

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World Wide Web page characteristics

In all, 21 (39%) World Wide Web pages did not report authors and 25 (46%) did not report sources of information or academic references. The majority of included World Wide Web pages (25; 46%) were published in the United Kingdom. All World Wide Web pages presented structured content. Almost two thirds of the World Wide Web pages (38; 70%) reported a privacy statement (Table 1).

Accuracy

A single World Wide Web page provided accurate information: evidenthycochrane.net. The median accuracy of included World Wide Web pages was 5 (interquartile range [IQR] 4-7). Included World Wide Web pages contained limited information (Table 1), skewed toward the diagnosis of endometriosis. Information pertaining to the medical or surgical management of pain or infertility associated with endometriosis was poorly represented. The most commonly reported recommendation, that clinicians should consider the diagnosis of endometriosis in the presence of gynecological symptoms such as dysmenorrhea, noncyclical pelvic pain, deep dyspareunia, infertility, or fatigue in the presence of any of the above, was described by four fifths of included World Wide Web pages (43, 80%). The least frequently described recommendations, described by a small minority of included World Wide Web pages (3; 6%) were: (1) in infertile women with endometriosis, clinicians may offer treatment with assisted reproductive technologies after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection; (2) clinicians should inform women with endometriosis requesting information on their risk of developing cancer that (a) there is no evidence that endometriosis causes cancer, and (b) there is no increase in overall incidence of cancer in women with endometriosis; and (3) some cancers (ovarian cancer and non-Hodgkin lymphoma) are slightly more common in women with endometriosis. The delivery of inaccurate, outdated, or dangerous information remains prevalent on World Wide Web pages. Inaccuracies included, first, "Your specialist may also suggest flushing out your blocked fallopian tubes. This procedure is an alternative to surgery and is usually successful" (World Wide Web page ID 17, Table 1). Routine tubal flushing is used in diagnostic evaluation of tubal patency and is not a recommended therapeutic approach.[25] A second inaccuracy we found was, "The only reliable

way to confirm the presence of the disease is by visually inspecting the abdominal organs by a procedure called a laparoscopy" (World Wide Web page ID 20, Table). There are many difficulties associated with visually confirming endometriosis. The most reliable ways to diagnose endometriosis are laparoscopy, biopsy, and histopathological examination. Visual diagnosis is no longer recommended.[19] The third inaccuracy we found was, "It is suspected that between 10-20% of reproductive aged women have the disease" (World Wide Web page ID 20, Table 1). The estimated prevalence within the general population is up to 10%.[19]

Credibility

Credibility was defined as a score ≥7. Sixteen World Wide Web pages (29%) were assessed as credible. The median credibility of included World Wide Web pages was 5 (IQR 2-8.8). The highest scoring criteria included context relevant to the disease and originality with all World Wide Web pages fulfilling these criteria. The least frequently described area of credibility was the discussion of content limitations, which was reported by 1 World Wide Web page (Table).

Quality assessment

Thirteen World Wide Web pages (24%) were assessed to be high quality, 40 (74%) were assessed to be of moderate quality, and 1 (2%) was assessed as low quality. The highest scoring criteria included describing aims (median 5; IQR 3-4) and being unbiased (median 5; IQR 4-5). World Wide Web pages typically did not describe the consequences of no treatment (median 1; IQR 1-1).

Readability

All included World Wide Web pages were assessed as fairly difficult to read (10th, 11th, and 12th grade), difficult to read (college), or very difficult to read (college graduate). The median readability score was 38.2 (IQR 30.7-48.0), indicating an average educational status of a college student would be required to understand the written content (Tables 1 and 2). In all, 45 World Wide Web pages (83%) presented written information at a level at or above college standard.

There were no substantial discrepancies between authors in the data extraction of quantitative parameters and we observed very high interrater agreement.

Comment

Summary

There are no World Wide Web pages that provide high-quality, accurate, and credible health information pertaining to endometriosis. Currently, World Wide Web pages contain limited amounts of information that are skewed toward the diagnosis of endometriosis. In the unlikely event that a World Wide Web page reports high-quality, accurate, and credible health information, it is typically written in language that is challenging for a lay audience to comprehend.

TABLE 2
Readability presented by US reading age

Ease of reading	US educational level	World Wide Web pages, n
Very easy (score 90–100)	5th Grade	0
Easy (score 80–90)	6th Grade	0
Fairly easy (score 70–80)	7th Grade	0
Plain English (score 60–70)	8th–9th Grade	1
Fairly difficult (score 50–60)	10th–12th Grade	8
Difficult (score 30–50)	College	32
Very difficult (score 0–30)	College graduate	13

Hirsch. Online endometriosis information. Am J Obstet Gynecol 2017.

Strengths and weaknesses

To our knowledge, this is the first study to examine the quality, credibility, accuracy, and readability of patient-focused online information pertaining to the diagnosis and management of endometriosis. We followed a robust, prospective systematic review method with validated instruments to assess the information presented. We evaluated individual World Wide Web pages using four validated instruments in a systematic process, independently performing all assessments in duplicate. We involved women with endometriosis, to inform the research question, design, and delivery of the research study, and its dissemination. All reviewers underwent recommended training prior to commencing the study.

This study is not without limitations. Limiting the search to the first 3 pages may have resulted in the exclusion of potentially eligible World Wide Web pages, however only 2.6% of people search past Googles' third page (www.protofuse.com). Included World Wide Web pages were only written in the English language, limiting the generalizability of our findings. The search was conducted while computer location services were disabled, however there may have been regional differences in search results, out of the authors control, which account for the predominance of British World Wide Web pages. We designed and registered this systematic review prospectively with a predefined inclusion criteria and analysis plan. There are few scientific publications that evaluate online information for patients allowing limited precedent to guide our methods. We observed diminishing returns, however this was not quantified. All World Wide Web pages were designed and managed within high-resource countries. This limits the applicability of this research to inform low-resource settings. We did not calculate weighted kappa to explore agreement between authors as the statistical level of agreement required in health research is unclear.[26] This evaluation is not currently recommended by the Cochrane Collaboration.[15] We could have conducted in-depth qualitative interviews of

women with endometriosis to explore their satisfaction with reading individual World Wide Web pages and evaluate the correlation with accuracy, credibility, quality, and readability.

Interpretation

As clinicians we must be aware that patients are increasingly seeking unregulated health information online that shapes opinions and treatment choices. The essence of modern clinical consultations is changing from a reliance on face-to-face interaction to information gathering online prior to seeking professional opinion. In the United States, there are >400,000 endometriosis searches per month in Google alone. We have demonstrated that individual World Wide Web pages are frequently incomplete, inaccurate, and poorly written. This is a barrier to patient education and results in those vulnerable patients who seek reliable information being misinformed. This is of greater importance to nonexpert patients (majority) who may be less able to evaluate the reliability of online information and be susceptible to the bias and inaccuracies contained within. These forays into online information gathering can lead to a breakdown in doctor-patient relationships. Inaccurate online health information can lead to clinicians advocating guideline-supported recommendations different from those read on reputable online sources. This mismatch of information can lead to a breakdown in trust in the clinician-patient relationship.

A review conducted by the US Office of Disease Prevention and Health Promotion (ODPHP) concluded that the potential for harm from inaccurate online information is significant.[27] Harm can be: (1) physical, from inappropriate treatments, adverse effects, or untreated disease; (2) emotional, from anxiety or false hope arising from inaccurate diagnostic, prognostic, or therapeutic information; and (3) financial, from costs incurred from unnecessary purchase of ineffective health services or products.[27] The ODPHP concluded that the Internet is critical to disease prevention, health promotion, and health care because of the increasing amount of information and services available via the Internet. This included a key objective to increase the quality of online health information.[28]

The readability of a World Wide Web page is an essential facet of online information. Information presented at a standard above patients' comprehension will limit its ability to inform the patient. Health care professionals should be aware that there is very limited information available to women with endometriosis with basic levels of literacy (indicates skills necessary to perform simple and everyday literacy activities), and therefore directing them to online information is of limited value in informing decision making.

Many online information rating systems use proxy markers for quality that do not consider the needs and opinions of patients and the public. Meric and colleagues[29] determined World Wide Web page popularity did not correlate well with traditional standards of World Wide Web page quality. Quality of online information is crucial as patients want to know about the risks, benefits, and uncertainty associated with diagnostic and therapeutic options. This information must be accurate to ensure that patients seeking information are gaining correct and complete information about the disease from up-to-date scientific evidence. Without access to good-quality information, patients are unable to make informed choices about their treatment.

Recommendations

Health care professionals and the wider medical community are increasingly quizzed by patients regarding health information found online. It is essential that health care professionals acknowledge their position of responsibility and proactively inform women with endometriosis about the risk of outdated, inaccurate, or even dangerous information online. Interactive consultations using online clinical practice guidelines such as those produced by the American Congress of Obstetricians and Gynecologists[30] or the Society of Obstetricians and Gynecologists of Canada[31] can provide the basis for clear, concise, evidence-based management discussions. Following consultations, patients should be advised of higher quality and more reliable sources of online information to answer questions they may have forgotten to ask during their limited consultation time.

While it may sound unrealistic to regulate health information on the Internet, codes of conduct have been developed and implemented. Health on the Net Foundation, based in the United States, provides accreditation to World Wide Web pages, which meet predefined standards related to readability, accessibility, and accuracy.[18] Information Standard, based in the United Kingdom, assesses online health information to ensure the information is clear, accurate, balanced, evidence based, and up to date. Information produced by the Royal College of Obstetricians and Gynecologists is accredited by this Information Standard (https://www.england.nhs.uk/tis/).

We acknowledge that regulating health information on the Internet has inherent difficulties as online authors are not bound by the same codes of practice as licensed health care professionals. The implementation of a robust Information Standard internationally will incentivize providers of online information to establish and adhere to codes of conduct ensuring an improvement in the quality of online information. Health care professionals and professional bodies should direct women with endometriosis toward higher quality, more reliable sources of online information. In general, World Wide Web pages that comply with the Information Standard should be prioritized.

The Internet will continue to increase its role as a provider of online health information. The media by which health information is transferred from source to patient should not compromise the fundamental features of accuracy, credibility, quality, and readability. It would not be tolerated if a health care professional were delivering substandard information in a face-to-face consultation. A strategy is required to improve the standard of online information for women with endometriosis with evident

need for the development of patient-focused online information with a robust evidence base. The translation of research from trials or systematic reviews into online sources has a direct pathway currently being delivered by Cochrane in the form of Evidently Cochrane summaries. These World Wide Web pages summarize Cochrane systematic reviews into patient-focused bite-size pieces of information.[32]

Conclusion

In the unlikely event that a World Wide Web page reports high-quality, accurate, and credible health information, it is typically challenging for a layaudience to comprehend. Health care professionals, and the wider community, should inform women with endometriosis of the risk of outdated, inaccurate, or even dangerous information online. Providers of online information should engage with established codes of conduct, such as the Information Standard. ■

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Appendix

Summary of European Society of Human Reproduction and Embryology guidelines for accuracy assessment

1. The guideline development group (GDG) recommends that clinicians should consider the diagnosis of endometriosis in the presence of gynecological symptoms such as: dysmenorrhea, noncyclical pelvic pain, deep dyspareunia, infertility, or fatigue in the presence of any of the above.
2. The GDG recommends that clinicians confirm positive laparoscopy by histology, since positive histology confirms the diagnosis of endometriosis, even though negative histology does not exclude it.
3. Clinicians are recommended to perform transvaginal sonography to diagnose or to exclude an ovarian endometrioma.
4. Clinicians are recommended not to use immunological biomarkers, including CA-125, in plasma, urine, or serum to diagnose endometriosis.
5. The GDG recommends clinicians to counsel women with symptoms presumed to be due to endometriosis thoroughly, and to empirically treat them with adequate analgesia, combined hormonal contraceptives, or progestagens.
6. Clinicians are recommended to prescribe hormonal treatment [hormonal contraceptives (level B), progestagens (level A), antiprogestagens (level A), or gonadotropin-releasing hormone agonists (level A)] as one of the options, as it reduces endometriosis-associated pain.
7. When endometriosis is identified at laparoscopy, clinicians are recommended to surgically treat endometriosis, as this is effective for reducing endometriosis-associated pain, ie, "see and treat."
8. When performing surgery in women with ovarian endometrioma, clinicians should perform cystectomy instead of drainage and coagulation, as cystectomy reduces endometriosis-associated pain.
9. The GDG recommends that clinicians refer women with suspected or diagnosed deep endometriosis to a center of expertise that offers all available treatments in a multidisciplinary context.
10. In infertile women with American Fertility Society/American Society for Reproductive Medicine stage I/II endometriosis, clinicians should perform operative laparoscopy (excision or ablation of the endometriosis lesions) including adhesiolysis, rather than performing diagnostic laparoscopy only, to increase ongoing pregnancy rates.
11. In infertile women with ovarian endometrioma undergoing surgery, clinicians should perform excision of the endometrioma capsule, instead of drainage and electrocoagulation of the endometrioma wall, to increase spontaneous pregnancy rates.
12. The GDG recommends that clinicians counsel women with endometrioma regarding the risks of reduced ovarian function after surgery and the possible loss of the ovary. The decision to proceed with surgery should be considered carefully if the woman has had previous ovarian surgery.
13. Clinicians can prescribe gonadotropin-releasing hormone agonists for a period of 3-6 months prior to treatment with assisted reproductive technologies to improve clinical pregnancy rates in infertile women with endometriosis.
14. In infertile women with endometriosis, clinicians may offer treatment with assisted reproductive technologies after surgery, since cumulative endometriosis recurrence rates are not increased after controlled ovarian stimulation for in vitro fertilization/intracytoplasmic sperm injection.
15. The GDG recommends that clinicians inform women with endometriosis requesting information on their risk of developing cancer that: (1) there is no evidence that endometriosis causes cancer, (2) there is no increase in overall incidence of cancer in women with endometriosis, and 3) some cancers (ovarian cancer and non-Hodgkin lymphoma) are slightly more common in women with endometriosis.

BMJ Open

Protocol for developing, disseminating and implementing a core outcome set for endometriosis

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ABSTRACT

Introduction: Endometriosis is a common gynaecological disease characterised by pain and subfertility. Randomised controlled trials evaluating treatments for endometriosis have reported many different outcomes and outcome measures. This variation restricts effective data synthesis limiting the usefulness of research to inform clinical practice. To address these methodological concerns, we aim to develop, disseminate and implement a core outcome set for endometriosis engaging with key stakeholders, including healthcare professionals, researchers and women with endometriosis.

Methods and analysis: An international steering group has been established, including healthcare professionals, researchers and patient representatives. Potential outcomes identified from a systematic review of the literature will be entered into a modified Delphi method. Key stakeholders will be invited to participate including healthcare professionals, researchers and women with endometriosis. Participants will be invited to score individual outcomes on a nine-point Likert scale anchored between 1 (not important) and 9 (critical). Repeated reflection and rescoring should promote whole and individual stakeholder group converge towards consensus, 'core', outcomes. High-quality outcome measures will be associated with core outcomes.

Ethics and dissemination: The implementation of a core outcome set for endometriosis within future clinical trials, systematic reviews and clinical guidelines will enhance the availability of comparable data to facilitate evidence-based patient care. This study was prospectively registered with Core Outcome Measures in Effectiveness Trials Initiative; number: 691.

INTRODUCTION

Endometriosis is a chronic inflammatory disease characterised by lesions of endometrial-like tissue outside the uterus that is associated with pelvic pain and/or infertility.[1] It is a common condition affecting women of reproductive age and may be associated with substantially reduced quality of life.[2] To address this considerable health burden novel treatments are continually being developed, which require robust evaluation. While significant effort has been paid to developing randomised controlled trial methods, the collection and reporting of outcomes and outcomes measures has been largely overlooked. The consequence of this is a plethora of differing outcomes that make drawing conclusions across a group of studies difficult and, sometimes, impossible.

We performed a systematic review of randomised trials evaluating treatments for endometriosis.[3] A total of 54 trials reported 164 different outcomes measured by 113 different definitions and instruments. The commonest pain outcome, dysmenorrhoea, was measured by ten different instruments. The commonest fertility outcome, pregnancy, was measured by three different definitions. The lack of consensus regarding the collection and reporting of outcomes prohibits the comparison and combination of individual trial data, limiting the usefulness of research to inform clinical practice.

The endometriosis research community has previously engaged with standardising important aspects of research design. The Art and Science of Endometriosis meeting, convened by the National Institutes of Health, has published recommendations regarding the standardisation of research design in several areas including entry criteria and outcome measures for pain symptoms.[4] The World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonization Project (WERF EPHect) has published tools for the standardisation of research design in several areas including clinical, covariate and surgical

phenotype recording and specimen collection, processing and storage.[5–8] Their work continues, involving global participants from a range of stakeholder groups including healthcare professionals, researchers, industry representatives and women with endometriosis, reflecting the enthusiasm of our specialty to work together to improve research design and clinical care.

The next challenge is to address the unwarranted, unhelpful and often confusing variation in outcome collection and reporting. The development and use of a core outcome set would help to address this challenge. Core outcome sets are well-defined, discriminatory and feasible outcomes routinely collected and reported in randomised trials and systematic reviews. They represent a minimum data set of outcomes selected and prioritised by key stakeholders including healthcare professionals, researchers and women with endometriosis.[9] The development and use of a core outcome set does not enforce harmony at the expense of innovation. The existence or use of a core outcome set does not imply that outcomes in an endometriosis trial should be restricted.[9] Rather, there is an expectation that the core outcomes will be collected and reported, making it easier for the results of trials to be compared, contrasted and combined as appropriate; while researchers continue to explore other outcomes as well.[10 11]

Recognising that the current inconsistency in outcome reporting is a serious hindrance to progress in our specialty, 80 editors of Women's Health journals have formed a consortium to support the development, dissemination and implementation of core outcome sets.[10] The Core Outcomes in Women's and Newborn Health (CROWN) initiative (http://www.crown-initiative.org) will support the dissemination and implementation of a core outcome set for endometriosis to increase the value of an initial research effort and ensure all future endometriosis trials report core outcomes and, therefore, routinely contribute data to important research questions.

Other specialties have succeeded in developing core outcome sets. An international initiative has developed a core outcome set for randomised trials evaluating interventions for chronic pain. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) has developed a core outcome set including six core outcome domains: (1) pain, (2) physical functioning, (3) emotional functioning, (4) participant ratings of improvement and satisfaction with treatment, (5) symptoms and adverse events and (6) participant disposition.[12]

Objective

We aim to produce, disseminate and implement a core outcome set for endometriosis.

METHODS AND ANALYSIS

Prospective registration

This study has been prospectively registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative, the registration number is 691 and is available online (http://www.comet-initiative.org/studies/details/691).

Steering group

An international steering group, including healthcare professionals, researchers and women with endometriosis, has been formed to guide the development of this core outcome set.

Scope of this core outcome set

The steering group has recommended the core outcome set should apply to clinical studies evaluating therapeutic interventions for women with endometriosis and follow established core outcome set development methodology (figure 1). All therapeutic interventions for endometriosis will be considered regardless of type, setting or mode of administration. We are not seeking to reach consensus regarding the standardisation of study design including other clinical, covariate and surgical phenotype recording nor specimen collection, processing and storage. The authors acknowledge the established tools in these areas.[5–8]

Step 1: identifying potential outcomes

We performed a systematic review of randomised trials evaluating therapeutic interventions for treatment of endometriosis.[5] We have extracted all outcomes and outcome measures reported within the trial reports. Working with patient and public representatives, we have developed lay definitions for these outcomes. The outcomes will be arranged into five domains: pain, subfertility, quality of life, harm and resource utilisation which, following the steering group's agreement, will be entered into a modified Delphi method.

Step 2: determining core outcomes

The core outcomes will be determined using a modified Delphi method. The method consists of a series of controlled rounds, where repeated surveys are administered.[13] The modified Delphi method facilitates repeated reflection and rescoring. This promotes whole and individual stakeholder group convergence on a consensus of 'core' outcomes and has advantages over less structured consensus methods. An online-modified Delphi method allows for scoring without the influence of dominant individuals or junior participants feeling obliged to agree with more senior members. Web-based Delphi surveys facilitate international participation and are considered feasible, efficient and acceptable to the user.[13 14] The modified Delphi method will be delivered within a web-based software hosted, designed and delivered by the University of Liverpool.

All key stakeholders will be invited to participate including gynaecologists managing pain or subfertility associated with endometriosis, chronic pain experts, health psychologists, family physicians, researchers and women with endometriosis. There are no clear recommendations

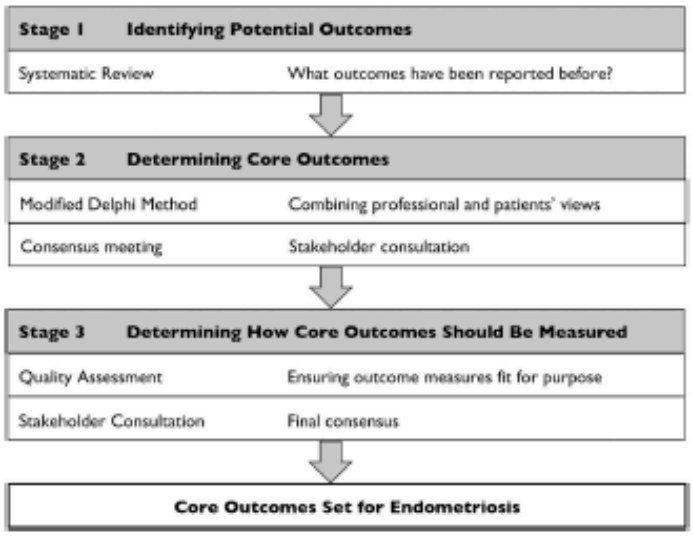

Figure 1 Study outline. This flow chart outlines the methods of core outcome set formation.

for calculating the required sample size; based on previous studies, we will aim to include a minimum of 18 participants from each stakeholder group.[15]

Delphi survey pilot

The Delphi survey will be developed to ensure the ease of completion using appropriate terminology and phrasing. The Delphi survey will be piloted by the study committee and a sample of stakeholders before it is accessible to all stakeholders.

Round 1

Participants will be asked to register online, provide demographic details and commit to both rounds (box 1). They will be allocated a unique identifier, which will anonymise their responses. Outcomes will be listed in five domains. Outcomes within each domain will be listed alphabetically, and participants will be asked to score individual outcomes using a nine-point Likert Scale anchored between 1 (not important) to 9 (critical). This scale was created by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group, and it has been widely adopted by core outcome set developers.[15] During the first round, participants will be invited to suggest additional outcomes. The round will close following a 4-week window.

For each outcome, the median and IQR of scores will be calculated and summarised graphically for the whole and individual stakeholder group responses using DelphiManager. Additional outcomes listed by participants will be reviewed by the steering committee and, if novel, listed in round 2.

Box 1 How do I contribute to improving endometriosis research?

The authors acknowledge the expertise and commitment of this journal's readership to improving patient care. They warmly invite readers to participate in the modified Delphi survey by registering their interest to participate here: http://www.eepurl.com/bNCo81

Round 2

Participants will be presented with individual stakeholder group response and asked to reflect on the similarities and differences observed before proceeding to score each outcome again. Additional outcomes proposed in round 1 of the Delphi survey will be added and scored once without reflection. The round will close following a 4-week window.

For each outcome, the median and IQR of scores will be summarised graphically by whole and individual stakeholder group response. A standardised definition of this round's results will enable individual outcomes to be classified:

1. *Consensus in (classify as a core outcome)*: over 70% of participants in each stakeholder group score this outcome domain 'critical' AND <15% of participants in each stakeholder group score outcome domain 'not important'.
2. *Consensus out (do not classify as a core outcome)*: over 70% of participants in each stakeholder group score outcome domain 'not important' AND <15% of participants in each stakeholder group score outcome domain 'critical'.
3. *No consensus (do not classify as a core outcome)*: anything else.[15]

In the unlikely event that there are more than ten core outcomes in a single domain the steering group will be able to alter the threshold for classification of consensus in. Round 2 results will be reviewed by the steering group to consider whether there is a need for a further Delphi survey round.

Step 3: stakeholder consultation

This final phase will involve a face-to-face meeting with key stakeholders. The meeting will include a range of views from participants that will be purposefully sampled from those who have completed all rounds of the Delphi study. The objective of the consensus meeting will be to discuss no consensus outcomes and a final core outcome set for endometriosis. A meeting is planned where the results from each round of the Delphi survey will be presented. To ensure unbiased consensus formation among a group of varied participants, the steering committee will ensure that the meeting is informal, inclusive, participatory and values all opinions.[14] To facilitate dissemination and implementation, we will invite editors from key journals, for example the *British Medical Journal*, and funders of endometriosis research.

Step 4: measuring core outcomes

Once core outcomes are agreed on, it will be important to determine how the outcomes should be measured.[16 17] Potential outcome measurement instruments will be evaluated following a consensus-based guideline for the selection of outcome measurement instruments for outcomes included in a core outcome set.[17] This involves a four-step process for the identification of outcome measurement instruments for an established set of core outcomes: (1) conceptual considerations; (2) finding existing outcome measurement instruments; (3) quality assessment of outcome measurement instruments and (4) generic recommendations for the selection of outcome measurement instruments for a core outcome set. This approach will ensure, for example, that all core outcomes will still be included in the highly unlikely event that all previous endometriosis studies failed to include a particular core outcome measure.

High-quality outcome measures will be associated with each core outcome. Where multiple high-quality instruments exist, priority will be given to instruments used within the WERF EPHect tools or core outcome measures for chronic pain clinical trials: IMMPACT recommendations.[4–8 12] If no high quality outcome instruments exist for a core outcome, this will be acknowledged.

ETHICS AND DISSEMINATION

Ethical review

We asked the advice of the National Research Ethics Service (NRES) about whether this study required ethical review by an NHS Research Ethics Committee, and they advised that this should be considered as service evaluation and development (see online supplementary appendix 1). All participants involved will be asked for their consent before participation in the Delphi study, and all procedures will be conducted according to the Declaration of Helsinki.

Dissemination

Implementing and disseminating a core outcome set for endometriosis in future clinical studies, systematic reviews and clinical guidelines could make a profound contribution to advancing the reach and relevance of research to inform clinical practice, enhance patient care and improve patient outcomes.

The selection of appropriate outcomes and outcome measures in future clinical trials is critical. The development of a core outcome set ensures that consensus outcomes important to all stakeholders, including patients, are routinely collected and reported. The Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) statement recommends the use of core outcome sets where they exist.[18] An endorsement by national and international funders, including National Institutes of Health, will facilitate (and fund) the collection and reporting of core outcomes.

The CROWN initiative, supported by 80 specialty journals, including the Cochrane Gynaecology and Fertility Group, has resolved to implement core outcome sets. Participating journals will require authors to report the results for core outcomes and offer conclusions based on these outcomes rather than non-core or surrogate outcomes.[19]

The production of high quantity and quality comparable data to be summarised within systematic reviews to inform clinical practice guidelines would be an important step forward for guideline developers. The National Institute of Clinical Excellence encourages the use of core outcomes sets where available when selecting outcomes during evidence scoping and synthesis. A core outcome set for endometriosis could directly influence national and international clinical practice.

CONCLUSION

The development of a core outcome set in endometriosis will enable the collection and reporting of a minimum data set important to all stakeholders, including women with endometriosis. Harmonising outcome collection and reporting for future clinical trials, systematic reviews and clinical guidelines will make a profound and important contribution to patient care.

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Full length article

Diagnostic accuracy of Cancer Antigen 125 (CA125) for endometriosis in symptomatic women: A multi-center study

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ABSTRACT

Study objective: To assess the diagnostic accuracy of serum Cancer Antigen 125 (CA 125) ≥ 30 units/milliliter (u/ml) for diagnosing endometriosis in symptomatic women.
Study design: Prospective observational cohort study including patients with symptoms of pelvic pain or subfertility undergoing elective diagnostic laparoscopy at two tertiary referral hospitals. We excluded patients suspected to have other gynecological pathology. We evaluated the accuracy of serum CA 125 (index test) with histologically confirmed endometriosis (reference standard).
Main results: Fifty-eight consecutive women recruited between October 2013 to March 2015. Women with endometriosis had a higher CA 125 level than those without endometriosis (mean 54.7 +/−71.6 vs 16.2 +/− 8.0). The specificity of CA 125 ≥ 30 u/ml was 96% (95% CI 81.7–99.9%) and sensitivity was 57% (95% CI 37.4–74.5%). The positive likelihood ratio for the histological presence of endometriosis with a CA 125 ≥ 30 u/ml was 15.8 (95% CI 2.3-112) providing a post-test probability of 94% (95% CI 71%–99%) in women with pelvic pain or subfertility. The area under the curve, 0.85 (95% CI 0.74–0.96) indicates high test accuracy.
Conclusions: CA 125 ≥ 30 u/ml is highly predictive of endometriosis in women with symptoms of pain and/or subfertility. CA 125 should be considered as a rule-in test for expediting the diagnosis and management of endometriosis, CA 125 < 30 u/ml is, however, unable to rule out endometriosis.

Introduction

Endometriosis is defined as the presence of functional endometrial like glands and stroma located outside the uterus. It is a disease clinically characterized by pain and associated with subfertility. The prevalence of endometriosis is estimated to be 10% in reproductive age women and up to 75% of symptomatic women [1]. The gold standard diagnostic test is visualization, biopsy and histological confirmation. Evaluation of non-invasive diagnostic biomarkers has not identified an accurate non-invasive test for the detection of endometriosis [2,3]. The development of a non-invasive rule in test for endometriosis could reduce time to diagnosis, provide psychological reassurance, offer treatment options, and reduce disease progression through earlier recourse to treatment [4]. Cancer Antigen 125 (CA 125), a well-established marker for epithelial cell ovarian cancer, is derived from coelomic epithelia including the endometrium, fallopian tube, ovary, and peritoneum [5]. CA 125 is raised in endometriosis through stimulation of coelomic epithelia [6]. Previous diagnostic accuracy studies have suffered from verification bias (visual diagnosis), design bias (case-control) or clinical heterogeneity (additional gynecological disease) [1].

We performed a prospective cohort study to evaluate the diagnostic accuracy of serum CA 125 for the presence of histologically confirmed endometriosis.

Methods

The regional and local ethics committee approval was sought for the study protocol. This study was conducted as a prospective

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observational cohort study (Research Ethics Committee reference number: 10/H0711/24). The cohort included women with pain symptoms and or subfertility undergoing laparoscopic investigation. We report the findings in accordance with the Standards for Reporting Diagnostic accuracy studies (STARD) [7]

Patient selection and data collection

All included participants signed a written informed consent form. The study recruited participants consecutively between October 2013 – March 2015. We prospectively collected clinical data from women referred for investigation of gynaecological pain symptoms and or subfertility cared for at The Royal London Hospital, London and St Bartholomew's Hospital, London. Both institutions are British Society for Gynaecological Endoscopy (BSGE) approved endometriosis centers with experience of diagnosing and managing women with endometriosis. The BSGE endometriosis centers need to fulfil a number of requirements including working in appropriate multidisciplinary clinical teams, auditing their outcomes and having sufficient workload to maintain their surgical skills [8].

Dysmenorrhea, dyspareunia or chronic pelvic pain was measured using visual analogue scales (VAS) 0–10 cm. This was chosen as it was the most frequently reported pain outcome measure in endometriosis trials [9]. The definition used for subfertility was unexplained failed conception after 12 months of regular unprotected vaginal intercourse [10]. Patients were excluded if they were believed to have or previously had a condition other than endometriosis which can cause a raised CA 125. These conditions included previous or suspected; leiomyoma, adenomyosis, pelvic inflammatory disease (PID), mature cystic teratoma, mucinous cystadenoma, and hydrosalpinges. These were evaluated with medical history and either ultrasound scan (USS) or magnetic resonance imaging (MRI). Women with a history of any malignancy or those who did not consent were excluded from analysis.

Participants were recruited and consented prior to surgery. Serum samples were collected preoperatively for CA 125 immunoassay measurement (Roche Diagnostics, Indianapolis, United States of America). The participants underwent routine operative surgical management of endometriosis from a consultant gynecologist on the same day. The surgeons performing the procedures were blinded to the result of the CA 125 test that was processed in a certified laboratory within 4 h of sampling with an automated immunoassay. Laparoscopy was performed and all recognizable endometriosis lesions were biopsied and then treated by either coagulation, excision, or ovarian cystectomy. In accordance with ESHRE guidance [11], histological confirmation of disease was attempted but not possible in all cases of suspected endometriosis. As the diagnosis of endometriosis has poor accuracy based on visual diagnosis alone [12], the authors decided to exclude those participants without histological confirmation of disease a priori. Those patients with visually confirmed endometriosis or other pelvic pathology at the time of surgery were excluded from the primary analysis.

Data were collected during face-to-face interviews with each patient by a single researcher (MH) in the preoperative assessment area. We collected general information for all participants including age, gravidity, parity, age at menarche, stage of menstrual cycle, smear history, previous surgery, medication, infertility duration, smoking status, alcohol status, and contraceptive use. Gynecological pain symptoms were assess using VAS 0–10 cm for dysmenorrhea, deep dyspareunia, and chronic pelvic pain, dyschezia, and dysuria. We did not control for the following confounders: hormonal use or stage of menstrual cycle.

The primary outcome was the diagnostic accuracy of CA 125 $\geq$ 30 u/ml to detect the presence of histologically confirmed endometriosis. Secondary outcomes included evaluating the gynecological pain symptoms between those with and without endometriosis.

Statistical analysis

Statistical data were collected in a computerized database and analyzed by SPSS software 18.0.0 (SPSS Inc., Chicago, Illinois). We compared the clinical characteristics between those with endometriosis and those without, summarizing the characteristics of the two groups using standard statistics. These two groups were classified as either reference standard (histological endometriosis) positive or negative. We then calculated the area under the receiver operating curve (ROC), which quantifies the ability of the index test (CA 125) to distinguish between patients with and without endometriosis. Our sample size was chosen so that if the true AUC was 0.85, we would be able to estimate it to within 0.15 using a 95% CI [13]. Positive likelihood ratios and negative likelihood ratios were calculated and post-test probability was evaluated using these likelihood ratios and Fagan's Nomogram [14] based on a pre-test prevalence estimate of 50% in this group of symptomatic women [15].

Results

Primary study

A total of 141 consecutive participants undergoing laparoscopy were approached for recruitment. 102 participants met the previously described inclusion criteria with sub-fertility and or gynecological pain symptoms. We prospectively recruited 67 women without evidence of previous fibroids, ovarian cysts (other than endometrioma), PID, adenomyosis, or hydrosalpinges. Nine patients were excluded at the time of surgery: biopsy of suspected lesions was not possible (n = 7); additional disease was noted (n = 1); and failed laparoscopic entry (=1). One study participant who did not undergo the procedure due to failed laparoscopic entry secondary to insufflation of the pre-peritoneal space. This prohibited safe primary trocar insertion. The patient was observed overnight and followed up in clinic without complication. Fifty-eight women were included in the primary analysis (Fig. 1). Of those included, 28 had no macroscopic pathology and 30 were found to have histologically confirmed endometriosis (Fig. 1).

Clinical characteristics

We excluded 84 participants for the following reasons; suspected adenomyosis, suspected leiomyoma, previous pelvic inflammatory disease or sexually transmitted infection, previous malignancy, and visually suspected endometriosis. A total off 58 participants were included for analysis. The clinical characteristics of the participants are summarized in Table 1. At the time of surgery, endometriosis was staged according the revised American Fertility Scoring for endometriosis and were classified as follows: 7 stage 1, 9 stage 2, 10 stage 3, 4 stage 4 [16]. Twenty-six participants were recruited during the follicular phase and 22 during the luteal phase of the menstrual cycle. We were unable to determine the phase of the menstrual in 10 participants due to hormonal contraceptive use.

Primary results

The mean age for those with confirmed endometriosis was 34.1 (SD+/− 5.9) and without endometriosis 32.2 (SD+/− 8.6).

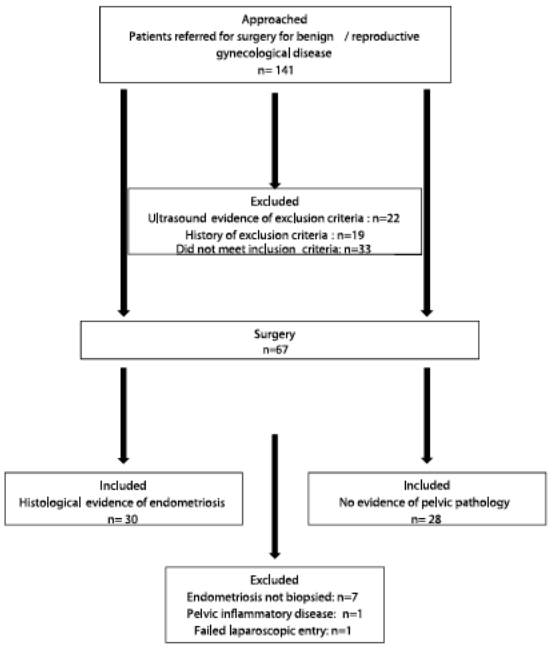

Fig. 1. Flow of included participants.

Study flow diagram.

Mean CA 125 values

Thirty participants diagnosed with endometriosis had a mean CA 125 level of 54.7 u/ml (SD 71.6). Twenty-eight participants with no macroscopic pathology had a mean CA 125 of 16.2 u/ml (SD 8.0). One patient had a CA 125 ≥ 30 u/ml without macroscopic gynecological disease while 17 had both a CA 125 ≥ 30 u/ml and histological endometriosis. Thirteen participants had a CA 125 < 30 u/ml in the presence of histological endometriosis while 27 had a CA 125 < 30 u/ml in the absence of macroscopic endometriosis.

Table 1
Participant Characteristics. Demographic participant details.

Baseline Characteristics	Endometriosis (n = 30)	Controls (n = 28)
Mean Age, yrs	34.1	32.2
Primary Infertility, n (%)	14 (47%)	8 (29%)
Secondary Infertility, n (%)	3 (10%)	6 (21%)
Endometriosis Stage I–II, n (%)	17 (57%)	–
Endometriosis Stage III–IV, n (%)	12 (40%)	–
Mean CA 125 value u/ml	54.7 (SD 71.6)	16.2 (SD 7.97)
Hormonal contraceptive use, n (%)	5 (17%)	4 (14%)
Preoperative pain score		
Mean VAS (0–10 cm) Dysmenorrhea	8.10 (SD 1.41)	6.49 (SD 2.97)
Mean VAS (0–10 cm) Dyspareunia	5.26 (SD 3.31)	4.53 (SD 3.79)
Mean VAS (0–10 cm) Dyschezia	3.77 (SD 3.41)	1.91 (SD 2.81)
Mean VAS (0–10 cm) Chronic pelvic pain	3.81 (SD 3.80)	4.24 (SD 3.82)
Mean VAS (0–10 cm) Dysuria	1.25 (SD 1.99)	0.73 (SD 1.72)

Diagnostic accuracy

Receiver operating characteristic curve (Fig. 2) demonstrates the accuracy of CA 125 ≥ 30 u/ml as a diagnostic test for endometriosis. The area under the curve, 0.85 (CI 0.74–0.96) indicates high test accuracy. The use of a predefined cut-off, CA 125 ≥ 30 u/ml is based on a previously published meta-analysis [1]. This will enable further data-synthesis in the future with a comparable cut off. The chosen cut-off value (30 u/ml) demonstrated 57% (95% CI 37.4–74.5%) sensitivity, 96% (95% CI 81.7–99.9%) specificity, and 76% diagnostic accuracy. The positive likelihood ratio is 15.8 (2.3–112) providing a high positive post-test probability of 94% amongst symptomatic women with CA 125 ≥ 30 u/ml (Fig. 3). The negative likelihood ratio is 0.45 [95% CI 0.30–0.68] producing a negative post-test probability of 33% in women with CA < 30 u/ml and common gynecological symptoms (Fig. 3).

Secondary results

Pain symptoms

We compared pain symptoms between those with endometriosis and those without endometriosis. Individual patient values were combined to produce means with standard deviations (SD) calculated. The mean VAS for dysmenorrhea amongst those

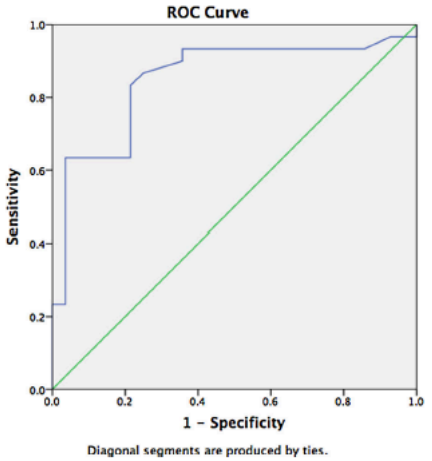

Fig. 2. Receiver Operating Characteristics Curve.
Sensitivity and specificity analysis of index test.

Area Under the Curve				
Test Result Variable(s): CA 125 u/ml				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.850	0.054	0.000	0.744	0.956

The test result variable(s): CA125 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
b. Null hypothesis: true area = 0.5

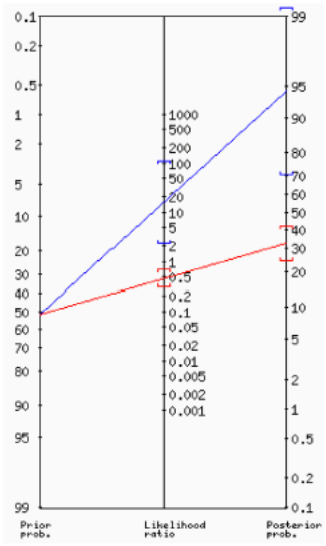

Fig. 3. Fagan's Nomogram.
Analysis of post-test probability.

Positive test:	
Positive Likelihood ratio:	15.75
95% confidence interval:	[2.26,112]
Post test probability (odds):	94% (17.1)
95% confidence interval:	[71%,99%]
Negative test:	
Negative Likelihood ratio:	0.45
95% confidence interval:	[0.30,0.68]
Post test probability (odds):	33% (0.5)
95% confidence interval:	[24%,42%]

women with endometriosis was 8.10 cm (SD 1.41 cm), and for women without endometriosis was 6.49 cm (SD 2.97 cm). The mean VAS for dyspareunia amongst those women with endometriosis was 5.26 cm (SD 3.31 cm), and for women without endometriosis was 4.53 cm (SD 3.79 cm). The mean VAS for chronic, non-cyclical pelvic pain amongst those women with endometriosis was 3.81 cm (SD 3.8 cm), and for those women without endometriosis was 4.24 cm (SD 3.82 cm) (Table 1).

Discussion

Main findings

This primary cohort study indicates that CA 125 ≥ 30 u/ml has a high accuracy for the detection of endometriosis in symptomatic women without evidence of other concurrent gynecological disease. CA 125 provides limited sensitivity for the detection of endometriosis and a negative test cannot exclude endometriosis. In the absence of other accurate biomarkers, CA 125 ≥ 30 u/ml provides diagnostic confidence to both clinicians and patients.

Area Under the Curve				
Test Result Variable(s): CA 125 u/ml				
Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.850	0.054	0.000	0.744	0.956

The test result variable(s): CA125 has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.
a. Under the nonparametric assumption
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Post test probability (odds):	94% (17.1)
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Negative test:	
Negative Likelihood ratio:	0.45
95% confidence interval:	[0.30,0.68]
Post test probability (odds):	33% (0.5)
95% confidence interval:	[24%,42%]

Strengths

This study has robust design with adequate power. We prospectively recruited a small homogenous cohort of women with pain or subfertility and no known additional disease. We reduced recruitment bias by limiting recruitment to a single researcher and assay bias was minimized by the use of a single quality controlled NHS laboratory. We blinded a select group of surgeons working at a endometriosis specialist center to the outcome of the index test result. We limited interpretation bias by using a pre-defined validated cut-off for the analysis. We addressed clinical heterogeneity by excluding participants with other gynecological diseases known to cause a raised CA 125.

Limitations

This study has limitations. We sampled the index and reference standard at varied times during the menstrual cycle amongst women, including those on hormonal modulators. Although there is no clear influence of menstrual timing [17] or hormones [18] altering CA 125 levels this introduces clinical heterogeneity. CA 125 is known to be raised in other benign and malignant gynecological pathology. We attempted to control for this by excluding all those patients with prior USS or MRI evidence of leiomyoma, adenomyosis, and hydrosalpinges, benign non-endometriotic cysts. We excluded those patients with a previous history of pelvic inflammatory or sexually transmitted disease. To minimize verification bias, the authors chose to restrict included patients to those with histologically confirmed endometriosis. This study was subsequently limited by the small number of included patients. There remain limitations with the reference standard (visualization and histological confirmation) used in this trial. The presence of occult microscopic endometriosis has been confirmed on visually normal peritoneum creating verification bias [19].

Comparison with existing literature

Previous primary studies and systematic reviews have demonstrated a limited role for the use of CA 125 in the detection of endometriosis. These studies suffered from significant verification bias (visual detection), design bias (case-control studies) and cohort heterogeneity (varied recruitment strategies) [1]. The sensitivity of CA 125 has repeatedly been demonstrated as poor with increasing accuracy associated with advancing stage of disease [1]. The search for an accurate non-invasive biomarker for endometriosis remains elusive [20,21] despite it being highlighted a research priority in 2009 [22].

Interpretation

As confirmed by Mol et al., 1998, CA 125 is an important biomarker with a role as a rule-in test for women with pain or subfertility [23]. The sensitivity of this test remains poor, limiting its use to cohorts of symptomatic women with a high pre-test prevalence. The diagnosis of women with pain or subfertility and a normal USS remains difficult and a CA 125 < 30 u/ml does not exclude endometriosis. Empirical use of the combined oral contraceptive pill remains an essential management strategy for women presenting with pain. This study demonstrates that when CA 125 ≥ 30 u/ml is used amongst a defined population with a narrow inclusion criteria for testing, a positive result provides a very high post-test probability. The high specificity minimizes false positive results and unnecessary treatment exposure from hormonal therapies or surgical procedures. The time from symptom onset to diagnosis and treatment remains a major concern for patients. The implementation of CA 125 in primary care or hospital settings as a point of care test for women with pain or subfertility and a normal USS may decrease delays in the diagnostic pathway, allowing women relief, liberation and legitimisation of their symptoms, together with access to support and an opportunity to discuss individualized medical or surgical management [1]. Further research is required amongst a population of women with pelvic pain or subfertility and a negative pelvic USS to assess its role in triaging treatment, access to specialist services, and reducing time to diagnosis or symptom control.

Conclusion

In the absence of a more accurate, non-invasive diagnostic test, CA 125 ≥ 30 u/ml can act as a rule-in test for the diagnosis of endometriosis amongst women presenting with symptoms of pain or subfertility.

Conflicts of interest

The authors report no conflicts of interest.

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Systematic review

Diagnosis and management of endometriosis: a systematic review of international and national guidelines

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Background The development of robust clinical guidelines requires standardised development methods informed by robust evidence synthesis.

Objectives We evaluated the methodological quality of endometriosis guidelines, mapped their recommendations, and explored the relationships between recommendations and research evidence.

Search strategy We searched EMBASE, MEDLINE, and PubMed from inception to February 2016.

Selection criteria We included guidelines related to the diagnosis and management of endometriosis.

Data collection and analysis The search strategy identified 879 titles and abstracts. We include two international and five national guidelines. Four independent authors assessed the methodological quality of the included guidelines, using the Appraisal of Guidelines for Research & Evaluation (AGREE-II) instrument, and systematically extracted the guideline recommendations and supporting research evidence.

Main results One hundred and fifty-two different recommendations were made. Ten recommendations (7%) were comparable across guidelines. The European Society of Human Reproduction and Embryology was objectively evaluated as the highest quality guideline (methodological quality score: 88/100). There was substantial variation between the supporting evidence presented by individual guidelines for comparable recommendations. Forty-two recommendations (28%) were not supported by research evidence. No guideline followed the standardised guideline development methods (AGREE-II).

Conclusions There is substantial variation in the recommendations and methodological quality of endometriosis guidelines. Future guidelines should be developed with reference to high-quality methods in consultation with key stakeholders, including women with endometriosis, ensuring that their scope can truly inform clinical practice and eliminate unwarranted and unjustified variations in clinical practice.

Keywords Clinical practice guidelines, diagnosis, endometriosis, systematic review.

Tweetable abstract #Endometriosis guidelines vary in recommendations and quality. @EndometriosisUK

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Introduction

Endometriosis is a benign gynaecological disease, characterised by pain and subfertility, associated with substantial reductions in quality of life.[1] The disease has three common

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manifestations, including peritoneal endometriosis, ovarian endometriosis, and deep infiltrating endometriosis.

The disease was first described in 1860, yet the aetiology and pathogenesis remain poorly understood.[2] Treatment strategies vary significantly between disease severity and the presenting symptoms of pain and/or subfertility.[3] These challenges have resulted in multidirectional research, with difficulties developing accurate diagnostic tests or effective therapeutic interventions because of variation and a lack of co-ordination along the research pipeline.[4] This variation limits the comparability of research to inform patient care through evidence synthesis in the context of guideline formation and patient information.[5]

Guidelines are systematically developed statements based on the synthesis of the best research evidence.[6] Their purpose is to improve patient care by informing clinical practice, reducing unwarranted variations in care, expediting the implementation of effective interventions, and eliminating ineffective interventions.[7,8] The generation of robust guideline recommendations requires standardised guideline development methods, including stakeholder engagement, quality assessment of research evidence, and consensus methods. The methodological quality of guidelines has been reported to be inconsistent.[9–11] Appropriate methodologies and rigorous strategies in the guideline development process are important for the successful implementation of the guideline recommendations.[12,13] Previous comparisons of national endometriosis guidelines were limited by scope, setting, and did not map recommendations and supporting evidence across individual guidelines.[14]

We evaluated the methodological quality of endometriosis guidelines, mapped their recommendations, and explored the relationships between recommendations and research evidence.

Methods

Sources

A protocol with explicitly defined objectives, criteria for guideline selection, and approaches assessing outcome selection was developed and registered with the International Prospective Register of Systematic Reviews (CRD42016036145). This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[15] Search terms were generated in consultation with healthcare professionals, researchers, and women with endometriosis. We searched EMBASE, MEDLINE, and PubMed, from inception to February 2016 (Appendix S1). We used the following search terms: consensus; endometrio*; endometriosis; guidance; and guideline.

Guideline selection

We organised the extracted guidelines and removed duplicates. Two reviewers (MB and MH) independently screened the full content of guidelines to assess eligibility, using a piloted data extraction tool. Any discrepancies between the reviewers were resolved by discussion. We included guidelines reporting recommendations for practice related to the diagnosis or management of endometriosis. We excluded guidelines for the following reasons:

- Local or regional guideline;
- Non-English language publication; and
- A more recent guideline available from the same authority.

Guideline characteristics

Two independent reviewers (MB and MH) extracted information, including: country of origin; year of publication; consensus method; stakeholders involved; disease area examined; description of database search; search terms used; language restriction; dates of searches; inclusion/exclusion criteria; and quality assessment instrument.[16]

Recommendations for clinical practice and supporting research evidence

Two independent reviewers (MB and MH) extracted and mapped the recommendation to five pre-specified domains:

- Diagnosis;
- Medical management for pain;
- Surgical management for pain;
- Medical management for infertility; and
- Surgical management for infertility.

References supporting clinical recommendations were retrieved and categorised according to the hierarchy of medical evidence:

- Cochrane review;
- Systematic review;
- Randomised control trials;
- Non-randomised control trials;
- Expert opinion; and
- No reference.

Discrepancies were resolved by discussion.

Assessment of methodological quality

Four reviewers (MB, JD, MH, and EP) underwent training in the use of the quality assessment instrument, Appraisal of Guidelines for Research & Evaluation II (AGREE-II).[15] Each reviewer independently assessed the quality of all included guidelines using the AGREE-II instrument. This validated assessment instrument contains 23 items grouped into six quality domains, with a seven-point Likert scale score, anchored between 1 (strongly disagree) and 7 (strongly agree), for each item.[17]

In addition, we assessed each guideline against six features of systematic review methodology:

- Named database search;
- Clearly defined search terms;

- Language restrictions;
- Dates of search;
- Detailed search strategy;
- Description of inclusion/exclusion criteria; and[14]

Discrepancies were resolved by discussion.[16]

Analysis

A total guideline score was calculated by the summation of its domains and standardised using a prescribed equation.[17] Guidelines were categorised in to low quality (0–33%), moderate quality (34–66%), and high quality (67–100%).

Tabulation and data

Descriptive statistics were calculated for all domains (median; range; interquartile range, IQR). We mapped the data for clinical recommendations, their supporting research evidence, and variation in clinical recommendations. The tables, appendices, and subcategories of presented information were developed in consultation with researchers, healthcare professionals, and women with endometriosis, within an iterative process. We subcategorised interventions according to the presenting symptom: pain or subfertility. Following this, interventions were further categorised to medical and surgical interventions by: disease severity; disease location; adjuncts to surgical management; and alternative treatments.

Results

Guideline search and selection

The search strategy identified 879 titles and abstracts. We screened 583 titles and abstracts following the exclusion of 296 duplicate records (Figure 1). We included two international and five national guidelines:

- American College of Obstetricians and Gynecologists (ACOG);
- Australasian Certificate of Reproductive Endocrinology and Infertility Consensus Expert Panel on Trial Evidence (ACCEPT);
- Collège National des Gynécologues et Obstétriciens Français (CNGOF);
- European Society of Human Reproduction and Embryology (ESHRE) Management of women with endometriosis;
- National German Guideline (S2k) Diagnosis and Treatment of Endometriosis (NGG);
- Society of Obstetricians and Gynaecologists of Canada (SOGC);
- World Endometriosis Society (WES) Consensus on current management of endometriosis.[24]

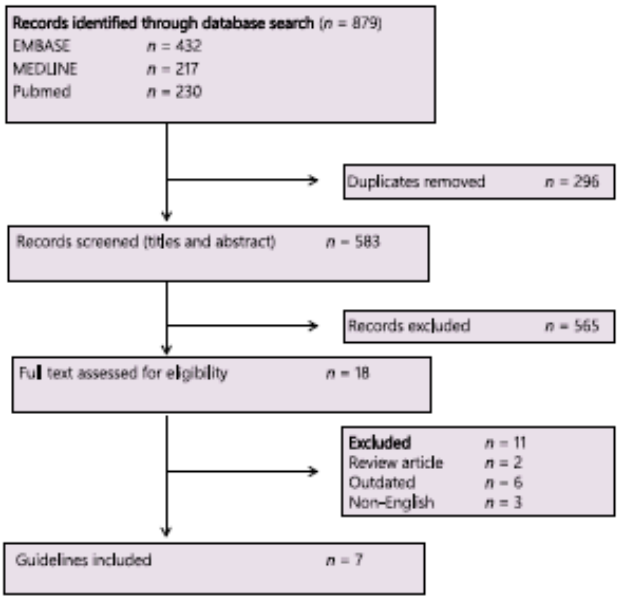

Figure 1. Flow of included guidelines.

Guideline characteristics

The included guidelines were published between 2006 and 2014.[18–24] Five of the guidelines were applicable to the diagnosis and management of pain and subfertility associated with endometriosis.[18,20–23] Two guidelines reported narrower scopes: the ACCEPT guideline addressed the management of subfertility associated with endometriosis and the WES guideline made recommendations with regards to the management of endometriosis.[19,24]

Between 15 and 56 individuals were involved in guideline development. Between one and four different stakeholder groups assisted in the development of the included guidelines. Three guidelines were developed in collaboration with women with endometriosis.[21,22,24] Two guidelines did not report the geographical location of their developers,[18,20] and one guideline was developed by individuals living in a single country.[23] All guidelines developed recommendations relevant to high-resource settings only.[25] Two guidelines explicitly defined a consensus development method, including the nominal group technique and modified Delphi method.[19,21] No guideline described a detailed search strategy to identify research evidence for use in recommendation formation. Five guidelines described methods to quality assess the research evidence.[18,19,21,23,24]

Recommendations for clinical practice

One hundred and fifty-two recommendations were identified and arranged into six clinical practice domains:

- Diagnosis (36 recommendations);
- Medical management for pain (30 recommendations);
- Surgical management for pain (39 recommendations);
- Assisted reproductive techniques for infertility (12 recommendations);
- Surgical management for infertility (22 recommendations); and
- Alternative treatments for pain and infertility (13 recommendations).

Ten recommendations (7%) were comparable across the included guidelines (Tables 1 and 2, and Tables S1–S4). Recommendations often varied across guidelines: for example, the ACOG and NGG guidelines stated different recommendations regarding the use of adjuvant hormonal therapy following the surgical management of endometriosis. The ACOG guideline recommended the use of postoperative gonadotrophin-releasing hormone analogues for the treatment of pain, whereas the NGG guideline does not recommend their use.

Thirty-six recommendations regarding the diagnosis of endometriosis were made across the included guidelines. Four recommendations were described by all guidelines, including:

- Biomarkers are not recommended for the diagnosis of endometriosis;
- Histological confirmation is recommended for the diagnosis of mild to moderate endometriosis (Table 2);
- Histology is recommended to confirm diagnosis; and
- Transvaginal ultrasound imaging is recommended for the diagnosis of endometrioma (Table S1).

Seventeen recommendations cited no research evidence or only cited expert opinion.

Table 1. Guideline recommendations for the diagnosis of endometriosis

	Mild/moderate endometriosis					Severe endometriosis					Endometrioma				
	Symptoms	Examination	Imaging	Biochemical	Surgical	Symptoms	Examination	Imaging	Biochemical	Surgical	Symptoms	Examination	Imaging	Biochemical	Surgical
Guideline															
ACOG (2010)[18]	•			•	•	•		•					•		
CNGOF (2006)[19]		•	•	•	•		•	•				•	•		
ESHRE (2014)[16]	•	•		•	•		•	•		•		•	•		•
NGG (2014)[21]			•	•	•		•	•				•	•	•	•
SOGC (2010)[22]	•	•	•	•	•	•	•	•	•			•	•	•	•

ACOG, The American Congress of Obstetricians and Gynecologists (2010); CNGOF, Collège National des Gynécologues et Obstétriciens Français (2006); ESHRE, European Society of Human Reproduction and Embryology (2014); NGG, National German Guideline: Guideline for the Diagnosis and Treatment of Endometriosis (2014); SOGC, The Society of Obstetricians and Gynaecologists of Canada (2010).
•: Recommendations.
*World Endometriosis Society (2013)[17] and Australasian CREI Consensus Expert Panel on Trial Evidence (2012)[18] provide no recommendations for the diagnosis of endometriosis.

Table 2. Level of evidence supporting recommendations

Guideline	Level of evidence				
	Cochrane review	Systematic review	Diagnostic accuracy trial	Expert opinion	No reference
Example 1. Biomarkers should not be used to diagnose endometriosis					
ACOG (2010)[18]			•		
CNGOF (2006)[20]					•
ESHRE (2014)[16]		•			
NGG (2014)[21]		•			
SOCG (2010)[22]		•			
Example 2. Diagnostic laparoscopy and histopathology should be used to diagnose endometriosis					
ACOG (2010)[18]					•
CNGOF (2006)[20]					•
ESHRE (2014)[16]				•	
NGG (2014)[21]		•	•		
SOCG (2010)[22]					•

ACOG, The American Congress of Obstetricians and Gynecologists (2010); CNGOF, Collège National des Gynécologues et Obstétriciens Français (2006); ESHRE, European Society of Human Reproduction and Embryology (2014); NGG, National German Guideline: Guideline for the Diagnosis and Treatment of Endometriosis (2014); SOGC, The Society of Obstetricians and Gynaecologists of Canada (2010).
•: Recommendation stated.
World Endometriosis Society (2013)[17] and Australasian CREI Consensus Expert Panel on Trial Evidence (2012)[19] provide no recommendations for the diagnosis of endometriosis.

Thirty recommendations regarding the medical management of endometriosis were made across the guidelines. Three recommendations were described by all guidelines:

- The combined oral contraceptive pill is recommended for endometriosis associated pain;
- Progestagens are recommended for endometriosis associated pain; and
- Gonadotropin-releasing hormone analogues are recommended for endometriosis associated pain (Table S4).

The strength of recommendations varied across the included guidelines (Table S1). Three recommendations cited no research evidence or only cited expert opinion.

Twenty-one recommendations were made with regards to the surgical management of infertility associated with endometriosis.[26–28] A single recommendation was described by all guidelines: surgery improves fertility with endometriosis-associated subfertility. Four recommendations cited no research evidence or only cited expert opinion (Table S5).

Recommendations relating to complementary and alternative interventions were infrequently discussed. Psychological interventions, for example mindfulness practice, were seldom reviewed (Table S4).

Research evidence supporting recommendations

The number of references cited in each guideline ranged from 0 to 211 (Tables S3–S5). The total number of Cochrane systematic reviews used within each guideline ranged from 0 to 25, and the number of randomised controlled trials used ranged from 0 to 28. Where available, we sought the original references used to generate recommendations and summarised the references and study design (Tables S3–S5).

Assessment of methodological quality

A systematic review was described by the majority of the guidelines.[18,19,21–24] No guideline explicitly described all six methodological features (Table 3). Three guidelines reported three features,[18,19,23] whereas the CNGOF guideline reported no features. No guideline reported a detailed search strategy or described explicit inclusion or exclusion criteria for the evidence that they sought.

Four guidelines did not report a consensus method.[18,20,23] Five guidelines reported the inclusion of multiple stakeholder groups;[19,21–24] however, only three guidelines clearly reported the inclusion of women with endometriosis in the development of the guidelines.[21,22,24] Quality assessment of the retrieved studies was described by five guidelines, with the assessment methods including:

- Grading of Recommendations Assessment, Development, and Evaluation;
- Canadian Task Force on Preventative Health Care;
- National Health and Medical Research Council; and
- United States Preventative Services Task Force.

Two guidelines were assessed as high quality,[21,24] four guidelines were assessed as moderate quality,[18,19,22,23] and one guideline was assessed as low quality (Table S2).[20]

Table 3. Guideline characteristics

Guideline (year)	Scope	Stakeholders (n; location)	Consensus method	Identification of evidence	Quality assessment of evidence
ACCEPT (2012)[19]	Infertility management Pain management	Healthcare professionals (36; unclear) Women with endometriosis (unclear) Pharmaceutical employees (unclear) Researchers (unclear)	Nominal group technique	Database: EMBASE; PubMed Search terms: reported Language: English Dates: not reported Detailed search strategy: not reported Inclusion/exclusion criteria: not reported	National Health and Medical Research Council
ACOG (2010)[18]	Infertility management Pain management	Not reported	Not reported	Database: ACOG; CENTRAL; MEDLINE Search terms: not reported Language: English Dates: 1985–2010 Detailed search strategy: not reported Inclusion/exclusion criteria: unclear	United States Preventative Services Task Force
CNGOF (2006)[20]	Diagnosis Infertility management Pain management	Not reported	Not reported	Database: not reported Search terms: not reported Language: not reported Dates: not reported Detailed search strategy: not reported Inclusion/exclusion criteria: not reported	Not reported
EHSRE (2014)[16]	Diagnosis Infertility management Pain management	Healthcare professionals (unclear) Women with endometriosis (1; one country) Pharmaceutical employees (unclear) Researchers (14; Europe; nine countries)	Nominal group technique Modified Delphi method	Database: CENTRAL; PubMed Search terms: not reported Language: not reported Dates: inception–January 2012 Detailed search strategy: not reported Inclusion/exclusion criteria: not reported	Grading of Recommendations Assessment, Development, and Evaluation (GRADE)
NGG (2014)[21]	Diagnosis Infertility management Pain management	Healthcare professionals (11; unclear) Women with endometriosis (unclear) Pharmaceutical employees (unclear) Researchers (21; Europe; five countries)	Not reported	Database: CENTRAL; MEDLINE; PubMed Search terms: not reported Language: not reported Dates: not reported Detailed search strategy: not reported Inclusion/exclusion criteria: not reported	Not reported
SOGC (2010)[22]	Infertility management Pain management	Healthcare professionals (unclear) Women with endometriosis (unclear) Pharmaceutical employees (unclear) Researchers (20; Canada)	Not reported	Database: CENTRAL; MEDLINE Search terms: not reported Language: English and french Dates: 1985–2010 Detailed search strategy: not reported Inclusion/exclusion criteria: not reported	Canadian Task Force on Preventative Health Care

Table 3. (Continued)

Guideline (year)	Scope	Stakeholders (n; location)	Consensus method	Identification of evidence	Quality assessment of evidence
WES (2013)[17]	Diagnosis Infertility management Pain management	Healthcare professionals (unclear) Women with endometriosis (unclear) Pharmaceutical employees (unclear) Researchers (56; international: 17 countries)	Unclear	Database: not reported Search terms: not reported Language: English Dates: 1985–2010 Detailed search strategy: not reported Inclusion/exclusion criteria: not reported	Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

ACCEPT, Australasian CREI Consensus Expert Panel on Trial Evidence (2012); ACOG, The American Congress of Obstetricians and Gynecologists (2010); CENTRAL, Cochrane Central Register of Controlled Trials; CNGOF, Collège National des Gynécologues et Obstétriciens Français (2006); ESHRE, European Society of Human Reproduction and Embryology (2014); NGS, National German Guideline: Guideline for the Diagnosis and Treatment of Endometriosis (2014); SD, Standard deviation; SOGC, The Society of Obstetricians and Gynaecologists of Canada (2010); WES, World Endometriosis Society (2013).

Guidelines were typically of high quality in the domains of clarity and presentation and scope and purpose. Guidelines were of moderate quality in the domains of stakeholder involvement and rigour of development. Guidelines were of low quality in the domains of applicability and editorial independence.

Discussion

Main findings

There is significant variation in endometriosis guideline quality and recommendations. One hundred and fifty-two unique recommendations were reported across seven guidelines, but only ten recommendations were comparable. Nearly a third of recommendations were either unreferenced or were supported only by expert opinion. No guideline followed the standardised approach to guideline development described within the AGREE-II guideline. The involvement of women with endometriosis varied significantly, funding sources and conflicts of interest were poorly described, and there was poor reporting of applicability and editorial independence.

Strengths and limitations

The strengths of this systematic review include its originality, robust search strategy, and methodological design. To our knowledge, this is the first study to systematically appraise the methodological quality and to map the recommendations of endometriosis guidelines. There was good agreement between all four reviewers, with discrepancies resolved quickly through discussion. We involved a woman with endometriosis in the design and delivery of our research.

Our empirical evaluation is not without limitations. Methodological scoring has not been definitively associated with applicability and clinical practice implementation.[17,29] We did not calculate weighted kappa values to explore agreement between authors, as the statistical level of agreement required in health research is unclear, and it is not currently recommended by the Cochrane Collaboration.[16,30] We could have considered systematically reviewing the randomised controlled trials and systematic reviews to form a judgement on the appropriateness of guideline recommendations; however, this would be unlikely to yield substantial benefit in the context of the considerable resource allocation required.

Interpretation

Our findings justify the critical appraisal of endometriosis guidelines, especially in an area such as endometriosis management, where diagnosis and treatment strategies are deemed suboptimal.[31] With differences in guideline development methods it is not surprising to find a paucity of

comparable recommendations, with wide intra-guideline variation in the supporting research evidence. The observations and conclusions of this review are likely to be replicated across our specialty.

Guidelines should be developed by searching, collecting, and collating evidence to make judgements using robust consensus methods. The methods to achieve this in an unbiased manner are clearly described in the AGREE-II criteria. Variation in methods to identify and assess the included evidence could contribute to the variation in guideline recommendations. A recent Institute of Medicine report on guideline development and their worth in modern clinical practice highlights widespread methodological limitations in formation.[32] Consumers of endometriosis guidelines should be aware of their shortcomings, including a lack of stakeholder engagement, varied rigour of development, limited applicability, and suboptimal editorial independence. The development of guidelines without a standardised methodological process will lead to the omission of beneficial therapies, an increase in preventable harm, and suboptimal patient outcomes or experiences.[9]

Guideline development can be prohibited by the availability of research evidence to answer the questions raised.[33] The quality of randomised trials is also variable, with variation in outcome collection and reporting being a serious hindrance to progress in our speciality.[34,35] The development and use of a collection of well-defined, discriminatory, and feasible outcomes, termed a core outcome set, would help to address these issues.[36,37] The Core Outcomes in Women's and Newborn health (CROWN) initiative aims to optimise the collection and reporting of comparable data, improving the synthesis of evidence within clinical guidelines, to support coherent recommendations.[36] Forty-six core outcome sets are in development; however, reproductive medicine and benign gynaecology are currently underrepresented.[37] A core outcome set for endometriosis is currently in development.[38] Four core outcome sets have been completed, including preterm birth.[35,39]

These findings remain consistent with a previous study reporting the low quality of guidelines for pain associated with endometriosis.[14] Over the last decade, there has been limited progress in the development of endometriosis guidelines. Most guidelines were of low quality for the domain 'applicability'. This domain obtained remarkably low scores, as most guidelines did not discuss the topics of practical implementation, barriers to application, costs, and auditing criteria. These findings are of concern given the significant resources required to generate an ever-increasing body of guidelines.[40] Future endometriosis guidelines should pay close attention to implementation.

The development of guidelines is a resource-intensive process with eight different organisations developing endometriosis guidelines. A coordinated approach to guideline development would have clear benefits for professionals, researchers, and women with endometriosis.

A single guideline, following methods described in the AGREE-II instrument, would reduce the unwarranted and unjustified variations in clinical practice, and would improve clinical outcomes. We urge guideline development groups to work collaboratively in order to secure the maximum efficiency and quality through the process.[41]

Conclusion

There is substantial variation in the recommendations and methodological quality of endometriosis guidelines. Future guidelines should be developed with reference to high-quality methods, in consultation with key stakeholders, including women with endometriosis, ensuring that their scope can truly inform clinical practice and eliminate unwarranted and unjustified variations in clinical practice.

Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Contribution to authorship

MH, JMND, CJD, and CB were involved in the conception and design of the research protocol. MH designed the search strategy. EP, MRB, and MH undertook the screening of search results, paper retrieval, and study selection. EP, JMND, MRB, and MH extracted data and assessed the quality of the guidelines. Tables, figures, and appendices were designed by MH and JMND. Drafts of the manuscript were prepared by MH and JMND. All authors contributed to the drafts and final version of the manuscript and approved the final review.

Details of ethics approval

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Medical intervention for pain associated with endometriosis.

Table S2. Methodological quality of endometriosis guidelines.

Table S3. Summarised guideline recommendations for the medical and surgical treatment of subfertility associated with endometriosis.

Table S4. Summarised guideline recommendations for the medical and surgical treatment of endometriosis-associated pain.

Table S5. Summarised guideline recommendations for the diagnosis of endometriosis.

Appendix S1. Medline search strategy.

Video S1. Author insights. ■

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